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DEVELOPMENT OF MANAGEMENT OF PATIENTS WITH CHRONIC DIFFUSE LIVER DISEASES WHO HAVE HAD COVID - 19.

Monograph

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Аннотация

Целью данного исследования является разработка комплексной стратегии ведения пациентов с хроническими диффузными заболеваниями печени, перенесших COVID-19, с учетом особенностей патофизиологии обоих заболеваний. Хронические заболевания печени, такие как цирроз, хронический вирусный гепатит и неалкогольная жировая болезнь печени, значительно повышают риск тяжелого течения и неблагоприятных исходов COVID-19. Пандемия SARS-CoV-2 привела к необходимости пересмотра подходов к лечению таких пациентов, учитывая вирусную нагрузку, системное воспаление и иммунологические изменения, влияющие на течение хронической патологии печени. В данной монографии подробно рассмотрены аспекты диагностики, мониторинга и лечения, включая необходимость модификации стандартных терапевтических протоколов, роли противовоспалительной и противовирусной терапии, а также управления осложнениями. Отдельное внимание уделено профилактическим мерам, направленным на минимизацию риска обострений и предотвращение декомпенсации заболеваний. Результаты исследования могут способствовать улучшению качества медицинской помощи и снижению смертности среди пациентов с хроническими заболеваниями печени, перенесших COVID-19.

Annotation

Ushbu tadqiqotning maqsadi ikkala kasallikning patofiziologiyasini hisobga olgan holda, COVID-19 bilan kasallangan surunkali diffuz jigar kasalliklari bilan og`rigan bemorlarni boshqarish bo`yicha kompleks strategiyani ishlab chiqishdan iborat. Jigar sir r ozi, surunkali virusli gepatit va alkogolsiz yog'li jigar kasalligi kabi surunkali jigar kasalliklari og`ir kasallik va COVID-19 ning salbiy oqibatlari xavfini sezilarli darajada oshiradi. SARS-CoV-2 pandemic keldi. Ushbu monografiya diagnostika, monitoring va davolashning aspektlari, shu jumladan standart terapevtik protokollarni o`zgartirish zarurati,

yallig`lanishga qarshi va virusga qarshi terapiyaning roli va asoratlarni boshqarish batafsil muhokama qilinadi. Kasallikning kuchayishi xavfini minimallashtirish va dekompensatsiyalanishining oldini olishga qaratilgan profilaktika choralariga alohida e`tibor qaratilmoqda. Tadqiqot natijalari COVID-19 bilan kasallangan surunkali jigar kasalligi bo'lgan bemorlarning tibbiy yordam sifatini yaxshilashga va o'limni kamaytirishga yordam beradi.

Abstract

The aim of this study is to develop a comprehensive strategy for managing patients with chronic diffuse liver diseases who have had COVID-19, taking into account the pathophysiology of both diseases. Chronic liver diseases such as cirrhosis, chronic viral hepatitis, and non-alcoholic fatty liver disease significantly increase the risk of severe course and adverse outcomes of COVID-19. The SARS-CoV-2 pandemic has led to the need to revise approaches to the treatment of such patients, taking into account the viral load, systemic inflammation, and immunological changes affecting the course of chronic liver pathology. This paper discusses in detail the aspects of diagnosis, monitoring, and treatment, including the need to modify standard therapeutic protocols, the role of anti-inflammatory and antiviral therapy, and the management of complications. Particular attention is paid to preventive measures aimed at minimizing the risk of exacerbations and preventing decompensation of diseases. The results of the study can help improve the quality of medical care and reduce mortality among patients with chronic liver diseases who have had COVID-19.

Abbreviations

AG – arterial hypertension.

ALT – alanine aminotransferase.

AST – aspartate aminotransferase.

ACE2 – angiotensin-converting enzyme.

VRVP – esophageal varices

GGT – gamma-glutamyltransferase.

BBB – blood-brain barrier.

ELISA – enzyme-linked immunosorbent assay.

ALF – Acuteliver failure.

ARDS – acute respiratory distress syndrome.

ARI – acute respiratory viral infections.

CDLD – chronic diffuse liver disease.

CLD – chronic lung disease.

CRF – chronic respiratory failure.

ALP – alkaline phosphatase .

NAFLD – non-alcoholic fatty liver disease.

NASH – non-alcoholic steatohepatitis.

CHAPTER I. LITERATURE REVIEW
FEATURES OF THE COURSE AND DIAGNOSIS OF EXACERBATION OF CHRONIC LIVER DISEASES AFTER COVID -19

1.1 Normal anatomy and physiology of the liver and its structural changes in various pathologies

Normal anatomy and physiology of the liver: features of adults and children

The liver is one of the largest organs in the human body, performing many functions including metabolic, synthetic, detoxifying, immune and endocrine. It plays a central role in maintaining homeostasis and has a unique ability to regenerate (Fig. 1.1).

General characteristics

- **The liver weight in adults** ranges from 1.2 to 1.5 kg, which is approximately 2-3% of body weight.
- **Liver mass in children** : relatively larger – about 4-5% of body mass in newborns, with a gradual decrease in relative weight as they grow.

1. Anatomy of the liver

1.1. Macroscopic anatomy

The liver is located in the upper right quadrant of the abdominal cavity below the diaphragm and is protected by the ribs.

1. **Liver lobes** :

- The liver consists of two main lobes - **the right** (larger) and **the left** , separated by the falciform ligament.
- Also distinguished are **the caudate lobe** and **the quadrate lobe** , which functionally belong to the right lobe.

2. **Glisson's capsule** :

Glisson's capsule is a connective tissue membrane of the liver, covering its surface and penetrating into the organ together with vessels, bile ducts and

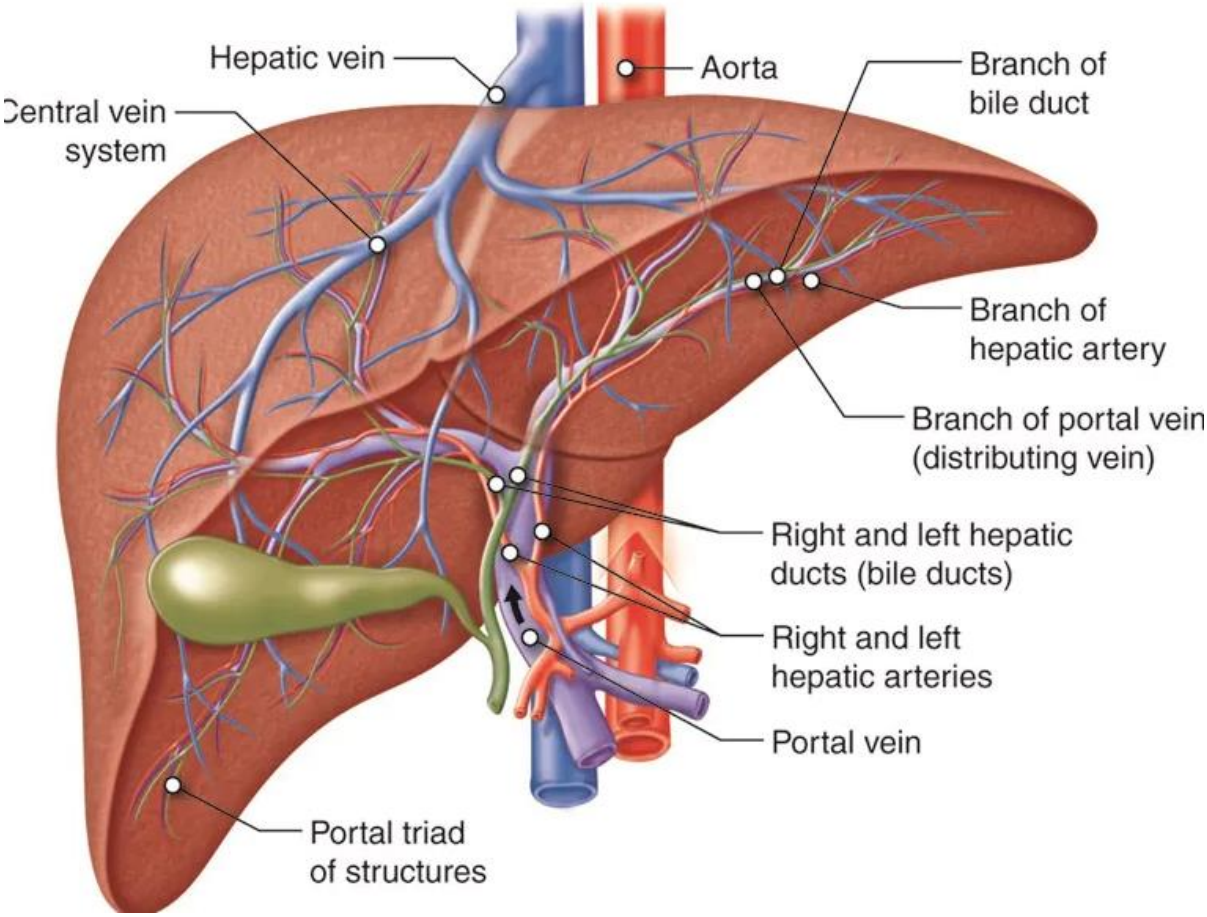


Fig. 1.1 Liver anatomy

nerves. It consists of dense fibrous tissue and contains collagen and elastic fibers, providing strength and elasticity. Inside the liver, the capsule forms connective tissue partitions (trabeculae), dividing the parenchyma into lobules. It performs a protective function, supports the structure of the liver and participates in the distribution of vessels and bile ducts.

3. **Blood supply** :

- *The liver receives blood from two sources:*

▪ **The portal vein (vena portae)** brings 70-80% of the blood rich in nutrients from the gastrointestinal tract. It is a large venous vessel that collects blood from the unpaired organs of the abdominal cavity (stomach, intestines, spleen, pancreas) and carries it to the liver for detoxification and metabolic processing. It is formed by the fusion of the superior mesenteric, inferior mesenteric and splenic veins. It passes as part of the hepatic ligament and enters the porta hepatis, where it branches into small branches, forming a network of

sinusoidal capillaries. Morphologically, it consists of a powerful vascular wall with a developed muscular layer, providing regulation of blood flow.

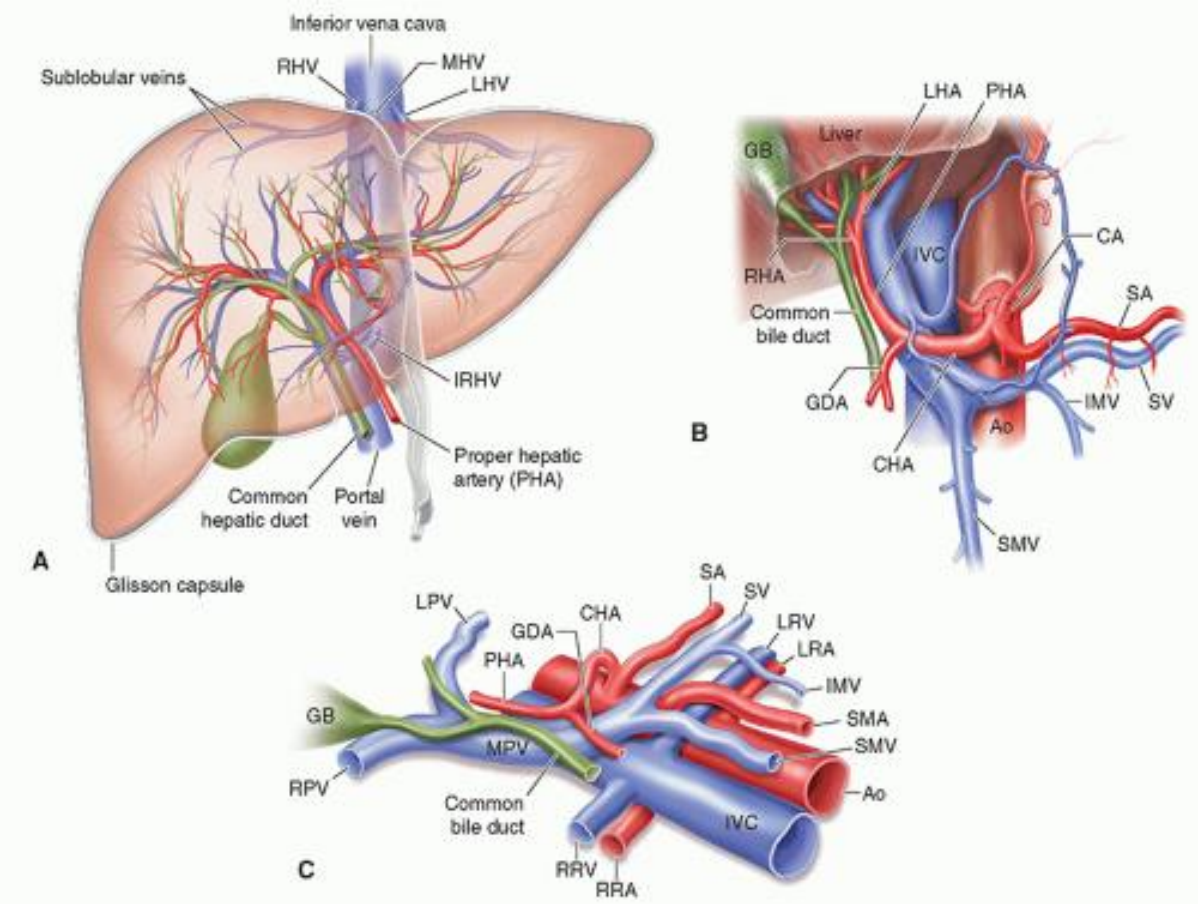


Fig. 1.2. Vascular anatomy of the liver. A: Intrahepatic distribution of the hepatic arteries, hepatic veins, portal veins, and biliary ducts. An accessory or inferior right hepatic vein is illustrated draining directly into the IVC and is a variant identified in some patients. B: The vessels and ducts of the upper abdomen. C: A recumbent view of the relationship between the vessels and ducts of the upper abdomen.

- **Hepatic artery (arteria hepatica)** – provides 20-30% of oxygenated blood. Usually is a branch of the celiac trunk (truncus coeliacus), but may have variations in origin. In the area of the liver gates, it divides into right and left branches, which branch inside the organ, following together with the portal vein and bile ducts. Morphologically, it consists of three layers: endothelium, a developed muscular layer and an external connective tissue membrane,

providing strength and elasticity of the vessel. Participates in the blood supply of the liver parenchyma and intrahepatic bile ducts.

- ***Venous outflow*** is carried out through **the hepatic veins** , which flow into the inferior vena cava. Usually there are three of them - right, middle and left, although there may be additional small branches. They are formed from the confluence of intrahepatic venous vessels that collect blood from the liver sinusoids, where it mixes from the portal vein and hepatic artery. Morphologically, the hepatic veins have a thin but strong wall with a pronounced endothelial layer and a poorly developed muscular layer, since the blood flow in them is passive. In the area of the confluence with the inferior vena cava, they do not have valves, which ensures free blood flow.

4. **Bile ducts** :

- Intrahepatic ducts start from the bile capillaries, merge into segmental, then into lobar (right and left), which form the common hepatic duct and their function is the formation of bile. Extrahepatic pathways include the common hepatic, cystic and common bile ducts, which flow into the duodenum through the Vater's papilla. Morphologically, the wall of the ducts consists of mucous with cylindrical epithelium, a muscular layer providing tone, and an external connective tissue membrane. They regulate the transport of bile and prevent its stagnation.

1.2. Microscopic anatomy

1. **Liver lobes (acini)** :

- The basic structural unit of the liver is the hexagonal lobe, which contains the central vein.
- Between the lobes are located portal tracts, consisting of :
  - Veins (branch of the portal vein).
  - Arteries (branch of the hepatic artery).
  - Bile duct.

2. **Cellular composition** :

- **Hepatocytes** : the main cells, making up 70-80% of the liver mass, perform most of the functions of the organ. Hepatocytes are the main parenchymatous cells of the liver, performing metabolic, detoxifying and secretory functions. They have a polygonal shape and are organized into hepatic beams, between which sinusoidal capillaries pass. Each cell contains one or two nuclei, developed granular and agranular endoplasmic reticulum, mitochondria, Golgi apparatus and inclusions of glycogen and lipids. Morphologically, hepatocytes have polarity: the basal part contacts the sinusoids, and the apical part participates in the formation of bile canaliculi. These cells actively regenerate and play a key role in metabolism, protein and bile synthesis.
- **Kupffer cells** are specialized liver macrophages located on the inner surface of sinusoidal capillaries. They are part of the monocyte-macrophage system and perform a phagocytic function, absorbing old erythrocytes, toxins, bacteria and other foreign particles from the blood. Morphologically, Kupffer cells have a branched shape, a developed lysosomal apparatus, numerous vacuoles and microvilli, increasing the area of contact with blood. They participate in the immune response, regulation of inflammatory processes and iron metabolism, helping to maintain the body's homeostasis.
- **Stellate (Ito) cells** : these are specialized liver lipocytes located in the perisinusoidal space of Disse between hepatocytes and endothelial cells. In the normal state, they accumulate vitamin A in the form of lipid droplets, regulate blood flow in the sinusoids and maintain homeostasis of the extracellular matrix. Morphologically, they have a stellate shape with numerous processes, a developed endoplasmic reticulum and lipid inclusions. When the liver is damaged, they are activated, turning into myofibroblasts that synthesize collagen, which can lead to fibrosis and cirrhosis. They play a key role in liver regeneration and fibrogenesis processes.
- **Endothelial cells** : form sinusoids.

Peculiarities in children:

- In newborns, the liver is relatively larger (up to 40% occupies the right upper quadrant of the abdominal cavity).
- The vascular system is more developed, which ensures a high level of metabolism.
- Immaturity of enzymatic systems limits detoxification functions.

2 . Physiology of the liver

2.1. Metabolic functions

1. **Carbohydrate metabolism** :

- The liver is involved in regulating blood glucose levels:
  - Glycogenesis is the synthesis of glycogen from glucose.
  - Glycogenolysis is the breakdown of glycogen into glucose.
  - Gluconeogenesis is the synthesis of glucose from non-carbohydrate sources (eg, lactate).
- In adults, daily glucose production is about 150 g.

2. **Lipid metabolism** :

- Synthesis of lipoproteins, cholesterol, fatty acids and triglycerides.
- Beta oxidation of fatty acids for energy production.

3. **Protein metabolism** :

- Synthesis of plasma proteins (albumin, blood clotting factors, transport proteins).
- Deamination of amino acids to form ammonia, which is converted to urea (urea cycle).

Peculiarities in children :

- In newborns, gluconeogenesis processes are less developed, which makes them more vulnerable to hypoglycemia.
- Lipid metabolism in the liver of children is more intense due to the need to provide energy for growth.

2.2. *Detoxification functions*

- **Phase I** :

- Oxidation, reduction, hydrolysis (enzymes of the cytochrome P450 family).
- Converts fat-soluble substances into more polar compounds.

- **Phase II** :
  - Conjugation with glucuronic acid, sulfates, glutathione.
  - Provides removal of toxins, including bilirubin and drugs.

Peculiarities in children :

- In neonates, immaturity of the cytochrome P450 system limits the ability to metabolize some drugs.
- This explains the high incidence **of neonatal hyperbilirubinemia** (jaundice).

2.3. Synthetic function

1. Protein synthesis:
   - Albumin is the main plasma protein that regulates oncotic pressure.
   - Coagulation factors (II, VII, IX, X) are dependent on vitamin K.

2. Bile synthesis:

- The liver produces about 600–800 ml of bile per day in adults.
- Bile is necessary for the emulsification and absorption of fats.

Peculiarities in children :

- In newborns, bile production is reduced, which affects the digestion of fats.

2.4. Immune function

- **Kupffer cells** play a key role in the phagocytosis of bacteria coming from the gastrointestinal tract.
- The liver synthesizes acute phase proteins (C-reactive protein, complement), which participate in the immune response.

Peculiarities in children :

- Newborns have reduced liver immune function, making them more vulnerable to infections.

3. Age-related changes in the liver

- In adults, liver function remains stable until 60–70 years of age, after which the rate of regeneration and synthetic function decreases.
- In children, all functional systems gradually develop, reaching maturity by 12–14 years of age.

- **2.5. Hematopoietic function and blood coagulation factors**

The hematopoietic function of the liver is manifested mainly in the embryonic and early postnatal periods, when it is the main organ of hematopoiesis. In the early stages of intrauterine development (approximately from the 5th week of gestation), the liver begins to actively form erythrocytes containing fetal hemoglobin, and later - leukocytes and megakaryocytes, precursors of platelets. During this period, the liver acts as a hematopoietic organ, since the bone marrow is not yet sufficiently developed. Hepatocytes and stromal cells create a microenvironment that promotes the proliferation and differentiation of hematopoietic cells. Kupffer cells are involved in the utilization of old erythrocytes and the regulation of hematopoiesis, and Ito stellate cells can secrete growth factors that affect the development of hematopoietic cells. After birth, the main hematopoietic function passes to the bone marrow, but the liver retains a reserve capacity for hematopoiesis and, in some pathological conditions (for example, myelofibrosis or severe anemia), can reactivate hematopoietic processes, ensuring extramedullary hematopoiesis.

The hematopoietic function of the liver is not limited to hematopoiesis in the embryonic period, but also includes the synthesis of most blood coagulation factors, which plays a key role in maintaining hemostasis. Hepatocytes produce almost all proteins of the coagulation cascade, including fibrinogen (I), prothrombin (II), proconvertin (VII), Christmas factor (IX), Stuart-Prower factor (X), and anticoagulant proteins - antithrombin III, protein C and protein S. Many of these factors depend on vitamin K, which is necessary for their carboxylation and functional activity. Kupffer cells also participate in the regulation of coagulation, utilizing activated factors and fibrin complexes circulating in the

blood. In liver pathologies (cirrhosis, hepatitis), the balance between the coagulation and anticoagulation systems is disturbed, which can lead to both bleeding and thrombus formation. Thus, the liver performs not only hematopoietic, but also regulatory functions in the hemostasis system.

Statistics (according to foreign and domestic authors) :

- The adult liver recovers up to 70% of its mass within 6–12 weeks after resection (Behrns et al., 2020).
- In newborns, the liver makes up to 5% of body weight, while in adults it is about 2% (Ponosov V.A., 2018).
- Bile production in newborns is about 200–300 ml per day, gradually increasing with age (Sherlock S., Dooley J., 2011).

The liver, being the central organ of metabolism and detoxification, undergoes significant structural and functional changes when exposed to various pathological factors. These changes depend on the etiology, degree of damage and the organ's ability to regenerate.

In case of pathologies

1. Fatty liver disease (NAFLD and NASH)

Etiology :

The main causes are obesity, type 2 diabetes, metabolic syndrome and dyslipidemia. 25% of the world's population shows signs of non-alcoholic fatty liver disease (NAFLD).

Pathogenesis :

- The accumulation of lipids in hepatocytes causes their damage.
- Lipotoxicity provokes oxidative stress and inflammation.
- Progression to nonalcoholic steatohepatitis (NASH) is accompanied by fibrosis.

Structural changes :

- Enlargement of the liver (steatosis), which is detected in 60–90% of patients with NAFLD during ultrasound examination.
- Accumulation of fat vacuoles in the cytoplasm of hepatocytes.

- With progression - pericellular fibrosis and formation of regeneration nodes.

Physiological changes :

- Disorders of carbohydrate and lipid metabolism.
- Elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 40–60% of patients.

2. Alcohol-induced liver damage

Etiology :

Excessive alcohol consumption, exceeding 40–80 g of ethanol per day in men and 20–40 g in women, is the main cause of alcohol-induced liver damage.

Pathogenesis :

- Ethanol is metabolized into acetaldehyde, which has a toxic effect on hepatocytes.
- Activation of inflammatory pathways and oxidative stress leads to cell apoptosis.

Structural changes :

- Steatosis in the initial stage.
- Progression to alcoholic hepatitis with inflammation and necrosis of hepatocytes.
- Formation of regeneration nodes and bridging fibrosis in cirrhosis.

Physiological changes :

- Decreased synthetic function of the liver (hypoalbuminemia, coagulopathy).
- Increased levels of bilirubin and γ- glutamyl transferase (GGT).

Statistics:

Alcoholic hepatitis is diagnosed in 35% of chronic alcohol users , and cirrhosis develops in 10–15%.

3. Viral hepatitis (HBV, HCV)

Etiology :

Chronic infection with hepatitis B or C viruses. According to WHO,

approximately 296 million people worldwide are infected with HBV and 58 million with HCV.

Pathogenesis :

- Viral replication triggers an immune response that damages hepatocytes.
- Chronic inflammation stimulates fibrosis and can lead to cirrhosis or hepatocellular carcinoma.

Structural changes :

- Inflammation of the portal tracts and hepatocyte necrosis.
- Progressive fibrosis reaching the stage of cirrhosis (stage IV according to the METAVIR scale).
- Formation of regenerative nodes.

Physiological changes :

- Disruption of protein synthesis (decreased albumin levels).
- Increased levels of ALT and AST, often 2–3 times higher than normal.

Statistics:

About 20–30% of patients with chronic HCV infection develop cirrhosis within 20–30 years.

4. *Cirrhosis*

Etiology :

Cirrhosis is the end stage of many chronic liver diseases, including viral hepatitis, alcoholic liver injury, and NAFLD.

Pathogenesis :

- Chronic inflammation causes activation of Ito stellate cells, which synthesize collagen.
- Extensive fibrosis develops with disruption of the liver architecture.

Structural changes :

- Regeneration nodes surrounded by dense fibrous tissue.
- Impaired blood flow through the portal system (portal hypertension).
- Decreased volume of functioning parenchyma.

Physiological changes :

- Impaired detoxification (hyperammonemia).
- Development of coagulopathy due to decreased synthesis of coagulation factors.
- Ascites, encephalopathy.

Statistics :

Cirrhosis causes about 2 million deaths worldwide each year.

5. Hepatocellular carcinoma (HCC)

Etiology :

The main risk factors are cirrhosis, chronic HBV and HCV, aflatoxin, alcohol.

Pathogenesis :

- Constant inflammation and regeneration under conditions of chronic injury lead to mutations in the DNA of hepatocytes.
- These mutations promote uncontrolled cell proliferation.

Structural changes :

- Formation of tumor nodes, often against the background of cirrhotic liver.
- Vascular invasion and metastasis.

Physiological changes :

- Decreased synthetic function of the liver.
- Increased levels of alpha- fetoprotein (AFP) in 70% of patients.

Statistics:

HCC is the fifth leading cause of cancer death worldwide, with an annual mortality rate of approximately 830,000 people.

6. Autoimmune hepatitis (AIH)

Etiology:

Dysregulation of the immune system leads to T cells attacking their own hepatocytes. AIH occurs in 10-20 people per 100 thousand population.

Pathogenesis :

- Activation of the immune system causes chronic inflammation.
- Inflammation leads to fibrosis and cirrhosis if left untreated.

Structural changes :

- Lymphocytic infiltration of portal tracts.
- Formation of "rosettes" from degenerating hepatocytes.
- Fibrosis progressing to cirrhosis.

Physiological changes :

- Increased ALT, AST, gamma globulins .
- Presence of specific autoantibodies (ANA, SMA).

Structural and physiological changes in the liver in various pathologies include hepatocyte damage, inflammation, fibrosis, impaired blood supply, and loss of synthetic function. These changes range from reversible (eg, steatosis) to irreversible (cirrhosis, cancer). Effective diagnosis and treatment at early stages can significantly improve the prognosis of patients.

1.2 Impact of COVID -19 on the human body.

The impact of COVID-19 on the human body is complex and systemic, affecting almost all organs and systems. This is due to both the direct cytopathic effect of the SARS-CoV-2 virus and the indirect effect of the body's excessive immune response. The main route of virus penetration is through the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in the cells of the lungs, heart, kidneys, liver, vascular endothelium, intestines and other tissues. This distribution of receptors explains the multi-organ damage observed in COVID-19.

In the early stages, the infection affects the upper respiratory tract, but as it progresses, it penetrates the alveolar cells of the lungs, causing viral pneumonia. The main manifestation at this stage is acute respiratory distress syndrome (ARDS), accompanied by hypoxia, inflammation, and damage to the alveolar-capillary barrier. This leads to fluid accumulation in the lungs, decreased blood oxygenation, and the development of respiratory failure. At the same time, the virus activates the immune system, causing the release of proinflammatory cytokines such as IL-6, IL-1β, and TNF-α, which leads to the

development of a cytokine storm - an overactive inflammatory response that can affect tissues and organs.

The cardiovascular system is also significantly affected by COVID-19. SARS-CoV-2 causes damage to the vascular endothelium, which provokes vascular dysfunction, hypercoagulability and thrombus formation. These processes lead to the development of thromboembolism, heart attacks, strokes and microthrombosis, which are often detected in severe patients. In patients with a predisposition to cardiovascular diseases, the virus can cause myocarditis, arrhythmia and heart failure. In the liver, the virus can directly infect hepatocytes and cholangiocytes via ACE2, and also cause secondary damage due to hypoxia, systemic inflammation and drug toxicity, which is manifested by an increase in the levels of transaminases, bilirubin and alkaline phosphatase.

The kidneys are also vulnerable: the virus causes acute kidney injury (AKI) associated with hypoxia, inflammation, and microthrombosis, as well as direct damage to renal cells. The incidence of AKI in COVID-19 reaches 30–50% in hospitalized patients with severe disease. In the gastrointestinal tract, the virus can cause diarrhea, nausea, vomiting, and malabsorption, which is associated with damage to intestinal epithelial cells. At the same time, damage to the intestinal microflora aggravates systemic inflammation.

The nervous system is exposed to both direct exposure to the virus and the consequences of systemic inflammation. Patients experience neurological symptoms: headaches, loss of smell and taste, cognitive impairment, encephalitis, and even strokes. It is believed that the virus can penetrate the blood-brain barrier or the olfactory epithelium.

Patients with severe COVID-19 often develop sepsis and multiple organ failure. These conditions are associated with massive tissue damage and uncontrolled activation of the immune system. Mortality is especially high in people with comorbidities such as diabetes, hypertension, obesity, chronic lung, liver and kidney diseases. Inflammatory processes aggravate these pathologies, which increases the risk of death. Statistically, severe COVID-19 with the

development of multiple organ failure is observed in 15-20% of hospitalized patients, and mortality in this group can reach 40-60%.

COVID-19 is a multisystem disease that manifests as an acute respiratory infection with possible involvement of almost all organs. This requires a comprehensive approach to diagnosis and treatment aimed at preventing both direct viral damage and secondary complications associated with hypoxia, inflammation and thrombosis .

SARS CoV-2 primarily affects the lower respiratory tract, so its main target is the lungs. However, recently, there has been ample evidence that the virus also attacks other internal organs: the heart, blood vessels, liver, kidneys, brain, central nervous system, digestive system, and others [8].

There is evidence of the negative impact of COVID-19 on the development of cardiovascular pathology de novo. NSHendren et al. proposed to introduce a new term to describe the cardiac manifestations of COVID-19: acute COVID- 19 cardiovascular syndrome (ACovCS), which describes a wide range of cardiovascular and thrombotic complications of coronavirus infection [9]. Acute COVID-19-associated cardiovascular syndrome is represented by arrhythmias (atrial fibrillation, ventricular tachycardia and ventricular fibrillation), acute myocardial injury, fulminant myocarditis, pericardial effusion, cardiac tamponade, arterial and venous thromboembolism in the form of acute coronary syndrome, stroke, pulmonary embolism, deep vein thrombosis. Most patients have signs of pulmonary hypertension [10].

Observations have shown that patients with severe COVID-19 often have elevated levels of a blood biomarker released by damaged and dying heart muscle cells [11].

In the journal JAMA Cardiology, heart muscle damage was noted in nearly 20% of 416 patients examined in Wuhan hospitals. In the same intensive care unit, arrhythmia was noted in 44% of 36 patients [12].

The coronavirus seriously affects the lungs not only during COVID-19: a partial decrease in their function is also observed in recovered patients. When

examining people who had recovered from the coronavirus, Chinese doctors found a "ground glass" symptom in their lungs - a decrease in the transparency of the lung tissue, which indicates irreversible damage [13].

These ranged from blockages in the blood vessels in the alveoli to scarring of the lung tissue. "Fibrosis can stabilise and not change over time, that's true. Some patients may not recover their lung function completely, but the consequences of that won't be that significant," explains Professor Louise Wain of the University of Leicester. "But there are cases of progressive fibrosis, and that's the really dangerous thing, because sooner or later it kills." [14]

The elasticity and distensibility of lung tissue decreases, respiratory function is impaired, and oxygen access through the walls of the alveoli of the lungs to the blood vessels is impeded [15].

Pulmonary fibrosis is not treatable, as the scarring of lung tissue is irreversible. However, with timely diagnosis of pulmonary fibrosis, the progression of this disease can be slowed down and sometimes even stopped [16].

Changes in lung tissue lead to the development of CRF, secondary pulmonary hypertension of the pulmonary heart. Traction bronchiectasis is described in 27-52.5% of cases of NCI [17] - this is a subtype of bronchiectasis in which the bronchi expand due to mechanical stretching caused by fibrosis of the adjacent lung parenchyma. The formation of bronchiectasis is accelerated by invasive ventilation of the lungs [18]. Dilated bronchi lose the ability to effectively evacuate mucus, and damage to the structure of the bronchi and lungs can predispose to chronic cough and recurrent infections [19].

In some patients who died from COVID-19, pathologists at the University Hospital of Zurich found inflammation of the entire cell layer on the inside of the blood and lymphatic vessels (endothelium) of various organs during autopsy [20]. Scientists have concluded that the new coronavirus SARS-CoV-2 leads to general inflammation of the endothelium via ACE 2 receptors [21].

This in turn can lead to serious disturbances in its microcirculation, which can cause disturbances in the heart, pulmonary embolism, and blockage of blood vessels in the brain and intestinal tract. All this can lead to failure of internal organs and death of the patient [22].

Increased inflammatory background along with the possibility of penetration of SARS-CoV-2 virions through the BBB contributes to damage to the respiratory center in the brainstem, which aggravates hypoxia in patients with COVID-19. Hypoxia stimulates further damage to the nervous tissue and destruction of the BBB, which leads to the formation of a vicious circle of "viral pneumonia - brain hypoxia - damage to the respiratory center - increased hypoxia" and explains the frequent occurrence of neurological disorders with a severe course of infection [23].

Olfactory and gustatory dysfunctions are typical symptoms with mild to moderate forms of COVID-19. In a multicenter study, olfactory dysfunction was reported by 85.6% of patients, and gustatory dysfunction by 88.0%. Olfactory dysfunction appeared before other symptoms in 11.8% of cases. Among 18.2% of patients without nasal airway obstruction or rhinorrhea, hyposmia or anosmia was observed in 79.7%. SARS-CoV-2- associated anosmia may be a COVID-19-specific symptom [24]. Direct and indirect neurological manifestations of COVID-19 [25].

It is important to emphasize that anosmia/ageusia observed in most patients with COVID-19 can be explained not only by ischemic damage to the central nervous system or viral damage to neuronal cells in the olfactory bulbs, but also by a sharp increase in IL-6 concentrations in sensory neurons. As is known, IL-6 plays one of the key roles in the formation of a cytokine storm [26], contributing to the induction of acute phase proteins and activation of the blood coagulation cascade, disseminated intravascular coagulation [27].

As Belgian scientists have established, nerve cells serve as a kind of gateway for the coronavirus into the central nervous system. Through the endings of the olfactory nerve - the first of the cranial nerves responsible for

olfactory sensitivity - the coronavirus penetrates the brain and reaches the centers of autonomous respiration and heartbeat located in the medulla oblongata [28].

A typical connection between human coronaviruses and multiple sclerosis is noted. Thus, according to N. Arbour et al. M. Desforges et al., HCoV-OC43 RNA was more often observed in the brain of patients with multiple sclerosis [29]. Single nucleotide substitutions in HCoV-OC43 RNA were detected in the brain of MS patients, which suggested the possibility of HCoVOC43 "adaptation" to the "host" with subsequent direct or indirect effects on the brain.

The COVID-19 pandemic has a sharply negative impact on the condition of patients with neuromuscular disorders [30], Duchenne, Becker and other muscular dystrophies, and cerebellar ataxia [31].

COVID -19 infection can cause the loss of dopaminergic neurons in the substantia nigra of the brain and increase the risk of Parkinsonism and depression [32].

With COVID-19, various demyelinating lesions of the brain and spinal cord are observed: inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, inflammatory vasculopathy of the central nervous system, accompanied by an increase in the titer of antibodies to oligodendrocyte and myelin glycoproteins in the blood [33].

Guillain–Barré syndrome is an inflammatory polyradiculoneuropathy associated with viral infections. A review of 37 published cases of Guillain–Barré syndrome in COVID-19 showed that the median time from the onset of COVID-19 symptoms to the development of Guillain–Barré syndrome was 11 days. In 1/2 of cases, patients with Guillain–Barré syndrome had signs of demyelination. In 76% of patients with Guillain–Barré syndrome, abnormal albumin levels were found in the CSF, consistent with damage to the BBB [34].

When studying atypical pneumonia SARS, scientists found that the coronavirus is able to penetrate the brain through nerve cells. When one of the patients in Japan infected with the SARS-CoV-2 coronavirus had an epileptic

seizure, he was diagnosed with meningitis caused by the penetration of the coronavirus into the central nervous system [35].

This has given doctors cause for concern that in some patients the pathogen may penetrate the brainstem and damage the respiratory center there. This explains the sudden respiratory arrest in patients with COVID-19 , which was not preceded by respiratory problems due to the infection. It has not yet been possible to determine for sure whether SARS-CoV-2 can provoke a stroke or increase the risk of its development [36].

The effect of SARS-CoV-2 on testosterone levels and testicular hemodynamics has been proven. Total testosterone (Ts) in the blood serum and testicular hemodynamic parameters decreased, and testicular blood flow worsened. There is evidence that a significant number of hospitalized patients with coronavirus infection had androgenetic alopecia and prostate cancer, and this category of patients had a more severe course of infection and complications [37].

LE Lamb et al. observed the development of severe genitourinary symptoms in patients with de novo COVID-19, especially urinary frequency of more than 13 episodes per 24 hours and nocturia of more than 4 episodes per night. Some of the subjects also reported pain or discomfort associated with urination. Thus , the authors confirm the possibility of developing COVID-19-associated cystitis [38].

Acute renal failure may result from damage due to the cytokine storm syndrome or immune-mediated renal damage [39]. According to S. Fan et al., ACE-2 receptors were also found in testicular tissue and Leydig cells, which may also indicate a potential risk of damage [40]. ARF in COVID-19 occurs in 5-15% of cases and is associated with high mortality. According to Y. Cheng, out of 710 patients, 44% had proteinuria and hematuria, and 26.7% had hematuria upon admission. Increased levels of creatinine and nitrogenous waste in the blood serum were observed in 15.5% and 14.1% of patients. With the development of ARF, the mortality rate was more than 90% [41-43].

Some patients are diagnosed with mini-renal infarctions, which develop as a result of the death of part of the kidney tissue caused by a blockage of the renal artery. In 30 percent of COVID-19 patients, kidney function is limited to the point that they require dialysis [44-46].

An important finding was the isolation of the virus in the urine - today there are 2 main assumptions: this is the entry of the virus into the urine with blood when the renal tubules are damaged due to a cytokine storm; the virus is released into the urine directly from the urothelium due to the high number of ACE-2 receptors in the proximal convoluted tubules of the kidneys [47].

In severe cases of COVID-19, blood clots faster. According to a recent study conducted in Hamburg, many patients who died from COVID-19 had blood clotting disorders and arterial and pulmonary embolisms during autopsy [48].

1.3. Activation of chronic diseases with COVID -19.

Patients with metabolic disorders and chronic diseases are most susceptible to SARS - CoV -2. Systemic hyperimmune inflammation due to the "cytokine storm", cytopathic effects, hypoxia, and drug toxicity are considered among the factors of organ damage. SARS-CoV-2, interacting with ACE2 localized in the endothelium of blood vessels, causes the development of endothelial dysfunction, increased permeability, impaired microcirculation, the development of vascular thrombophilia and thrombus formation [49].

The key virulence factor is the interaction of the receptor-binding domain of the S protein, located on the outer membrane of SARS-CoV, with the angiotensin-converting enzyme 2 receptor, activated by human transmembrane serine proteases. ACE2 is expressed in surfactant secreted by type II alveolocytes from blood plasma components [50]. Surfactant is a surface-active monomolecular film that is located at the air-liquid interface in the alveoli, alveolar ducts and respiratory bronchioles of the 1st to 3rd order and prevents the alveolar walls from adhering during breathing [51]. ACE2 expression

protects against lung damage, but it is reduced due to its binding to the SARSCoV spike protein, which increases the risk of infection. Increased ACE2 expression does not exclude the possibility of increased binding to SARS-CoV. Up to three viruses can attach to one target [52].

Non-structural proteins of SARS-CoV are capable of modifying the structure of hemoglobin in the erythrocyte, which leads to a disruption of oxygen transport, causes iron dissociation, porphyrin formation, and an increase in ferritin. Such effects can lead to increased inflammatory processes in the lungs, oxidative stress, hypoxemia, hypoxia, the development of symptoms of acute respiratory distress syndrome (ARDS) and multiple organ oxygen deficiency [53].

SARS-CoV-2 is tropic to goblet cells contained in the mucous membrane of the respiratory tract, intestines, conjunctiva of the eyes, pancreatic ducts and parotid salivary glands. Active replication of the virus significantly reduces the protective functions of goblet cells (mucus formation), which also facilitates the penetration of the virus into the human body [54]. In response to the spread of coronavirus, the development of a hyperimmune reaction is observed, characterized by the synthesis of a significant amount of pro-inflammatory interleukins (IL-1β, IL-6, tumor necrosis factor) and chemokines with a simultaneous decrease in the content of T-lymphocytes in the blood [55].

Other host receptors and/or co-receptors that facilitate SARS-CoV-2 entry into humans. The UFO tyrosine kinase receptor (AXL) specifically interacts with the N-terminal S domain of SARS-CoV-2. Using both pseudotype SARS-CoV-2 and authentic SARS-CoV-2, overexpression of AXL in HEK293T cells facilitated SARS-CoV-2 entry as efficiently as ACE2 overexpression, while knockout of AXL significantly reduced SARS-CoV-2 infection in human cells and primary epithelial cells [56]. Soluble human recombinant AXL blocked SARS-CoV-2 infection in cells expressing high levels of AXL [57]. The expression level of AXL correlated well with the level of SARS-CoV-2 S in bronchoalveolar lavage fluid cells from COVID-19 patients. Taken together, the

results indicate that AXL is a novel candidate receptor for SARS-CoV-2 that may play an important role in the spread of viral infection and indicates that it is a potential target for future clinical intervention strategies [58].

With the emergence of new strains of coronavirus, the severity of the infection is constantly changing. There is evidence that the presence of chronic diseases leads to a worse development of the situation [59].

According to statistics, the highest number of deaths from coronavirus are among the elderly and patients with chronic pathologies.

In pathologies, there is already chronic inflammation in the bronchi. Against the background of coronavirus infection, the inflammatory process intensifies and spreads throughout the respiratory system.

ACE2 , a receptor for viral entry , in the airways [60]. A meta-analysis of 11 studies showed that this category has a 4.38 risk of severe COVID-19. Another meta-analysis [61], which included 7 studies and a total of 1,592 patients with COVID-19, also emphasized that COPD is associated with severe COVID-19 [61-62].

At the same time, coronavirus can cause more frequent attacks of broncho-obstruction, the development of asthmatic status, which in itself is a life-threatening condition. In chronic obstructive pulmonary disease, coronavirus damages lung tissue, which can lead to the rapid development of respiratory failure and, as a consequence, hypoxia. The risk of death in such pathologies is significantly higher [63].

Diabetes mellitus is one of the most important comorbidities associated with the severity of all three known pathogenic human coronavirus infections, including COVID-19. An international group of experts in diabetes and endocrinology notes that, depending on the global region, 20-50% of patients with COVID-19 had type 2 diabetes [64]. Currently, there is no evidence of an increased risk of developing COVID -19 in patients with type 1 diabetes. Patients with diabetes are characterized by a more rapid development of ARDS.

Preemptive administration of monoclonal antibodies for the treatment of “cytokine storm” has been previously justified [64-66].

Hypertension, coronary heart disease, heart attacks, strokes, arrhythmias, heart defects and atherosclerosis are very dangerous in themselves. With pneumonia, the body already suffers from oxygen deficiency, heart problems increase these risks many times over. In addition, COVID-19 often causes problems with the blood: it thickens, blood vessels can become blocked by blood clots in the brain (and, as a result, a stroke) or in the heart (heart attack) [58-67]. Mortality from acute MI accounts for 40% of the overall mortality of patients with COVID-19. Hypertension is one of the most common cardiovascular diseases in COVID-19. The presence of hypertension worsens the prognosis of patients with COVID-19 and increases the risk of death by more than 2 times [68]. The mechanisms of arrhythmia in COVID-19 include: metabolic disorders and hypoxia; hypokalemia; development of viral myocarditis with malignant tachyarrhythmias. Some drugs used in the treatment of COVID-19 may prolong the QT interval and increase the risk of torsades de pointes [68-71].

Cancer patients are seriously weakened, their immunity is suppressed - due to the disease or aggressive treatment methods (radiation, chemotherapy). Against the background of reduced immunity, any infections are dangerous for them, even ARVI. Especially coronavirus - it can provoke rapid and aggressive inflammation in the lungs, brain damage, the development of bacterial infections. These complications can lead to death [72].

In autoimmune pathologies, the human immune system attacks its own cells of various organs and tissues, which may require certain treatment methods - the use of immunosuppressants - drugs that suppress the activity of the body's own immune system. In the case of the development of coronavirus infection in such patients, it is very difficult to predict the response: their body has a harder time fighting COVID-19, so they usually endure the disease in a severe form [71-73].

1.4 Features of the clinical course of chronic pulmonary disease after COVID -19, their frequency, complications and mortality.

The clinical course features reflect the profound interaction between SARS-CoV-2 viral infection and pathological processes in the liver. COVID-19 has both a direct effect on hepatocytes and cholangiocytes via ACE2 receptors and an indirect effect via systemic inflammation, cytokine storm and hypercoagulation. In patients with CLD, such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, chronic viral hepatitis and cirrhosis, the course of COVID-19 often becomes more severe, and the post-COVID period is accompanied by the progression of fibrosis and deterioration of liver function. The incidence of exacerbation or decompensation of CLD after COVID-19 reaches 40-50%, especially among patients with cirrhosis or metabolic disorders (diabetes mellitus, obesity).

In patients with NAFLD, COVID-19 exacerbates lipotoxicity, inflammation, and oxidative stress, which leads to an accelerated transition of steatosis to steatohepatitis and fibrosis. Alcoholic liver disease after COVID-19 is often accompanied by increased inflammation, elevated transaminase levels, and an increased risk of alcoholic hepatitis. In patients with chronic viral hepatitis B and C (HBV and HCV), reactivation of viral infection is observed in 15-20% of cases, especially with immunosuppressive therapy. In patients with cirrhosis, COVID-19 increases the risk of decompensation, including the development of ascites, bleeding from esophageal varices (up to 15-20%), hepatic encephalopathy, and acute-chronic liver damage. The incidence of portal vein thrombosis in patients with cirrhosis who have had COVID-19 reaches 5–10%, which is associated with hypercoagulation against the background of systemic inflammation and endothelial damage.

Complications in patients with CDZD after COVID-19 include the development of sepsis, multiple organ failure, hyperactivation of fibrotic processes, and an increased risk of hepatocellular carcinoma. The incidence of

severe complications directly depends on the degree of liver damage before infection: in patients with decompensated cirrhosis, mortality reaches 30–40%, while in patients with compensated cirrhosis this figure decreases to 10–15%. According to research data, patients with CDZD have a 1.5–2 times higher risk of developing severe COVID-19 compared to the general population.

Pathophysiologically, COVID-19 leads to deterioration of liver function through activation of immune and inflammatory pathways, including hyperproduction of cytokines (IL-6, TNF-α), imbalance in the blood coagulation system, hypoxic injury and direct toxic effect of the virus on liver cells. These processes are accompanied by a decrease in the synthetic function of the liver, impaired detoxification and increased fibrosis. The prognosis of patients with CDLD after COVID-19 is determined by the degree of liver damage, age, the presence of comorbidities (e.g. cardiovascular or metabolic), as well as the effectiveness of treatment during the acute period of infection. These data highlight the need for a multidisciplinary approach to the management of such patients, including regular monitoring of liver function, the use of hepatoprotectors, correction of metabolic disorders and thrombosis prevention to improve the prognosis and prevent complications.

There are many possible harmful effects of coronavirus infection on the liver. It is no secret that SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE-2) in its receptor role to penetrate the intracellular environment. It has been found that ACE-2 is expressed to a greater extent on cholangiocytes, which makes the liver a possible target for the virus [74]. Liver biopsy in patients with atypical pneumonia with SARS-CoV 2002 indicated a large increase in mitotic cells with eosinophilic bodies and balloon-like hepatocytes, which suggested the idea that SARS-CoV can induce hepatocyte apoptosis and provoke liver damage. Many studies have shown that SARS-CoV, through its specific protein 7a, can induce apoptosis at the subcellular levels of various organs (including lung, kidney, and liver) in a caspase-dependent manner, suggesting that SARSCoV may directly affect liver tissue [75]. Especially, abnormal serum

cytokine and chemokine thresholds were found in patients at the early stage of SARS-CoV infection: the serum levels of IL-1, IL-6, and IL-10 in patients with chronic diffuse liver diseases were higher than in patients with normal or slightly reduced liver function, suggesting a reasonable correlation between liver damage and inflammatory responses caused by coronavirus infection. In addition, SARS patients with HBV/HCV infection were more resistant to liver damage changes, and severe hepatitis is usually associated with increased hepatitis virus replication during SARS-CoV infection [76]. Although equitable data on SARS-CoV-2 are not achieved, chronic viral hepatitis does not appear to increase the likelihood of severe prognosis in COVID-19 [76-78]. COVID-19-associated hepatocellular injury is mainly characterized by mild steatosis, lobular and portal inflammation, foci of apoptosis/necrosis, and elevated plasma ALT and AST (upper left panel). Preliminary observations suggest that the injury may be caused by hepatocellular infection with direct cytopathic effects of SARS-CoV-2, which may induce mitochondrial dysfunction and endoplasmic reticulum stress, promoting steatosis. In addition, SARS-CoV-2 infection can also activate mTOR (Mammalian target of rapamycin), which ultimately inhibits autophagy (as a mechanism for viral degradation) and promotes viral egress from the immune system [79]. In addition, cytokine storm, hypoxic conditions due to ARDS and drug-induced liver injury (DILI) may contribute. COVID-19-associated cholangiocellular injury has also been observed, which is mainly characterized by bile duct proliferation, sometimes by bile plug formation and increased plasma γGT and ALP [62-65]. Systemic viral infections are partly associated with transient increases in transaminases, which may reflect generalized immune activation or inflammation caused by circulating cytokines without liver dysfunction, the so-called “bystander hepatitis” phenomenon.

Liver damage in Covid-19 occurs entirely due to hypoxia (oxygen depletion), developing against the background of pulmonary failure. Hypoxemia, which occurs with aggravated pneumonia, causes ischemic liver

damage in patients with coronavirus infection. A decrease in oxygen content in the body under hypoxic conditions can lead to the death of liver cells [16-28].

The liver plays an important role in regulating immune homeostasis. Patients with CLD, especially those with cirrhosis, may have dysregulated innate and adaptive immunity and may therefore be at higher risk of SARS-CoV-2 infection, COVID-19-related complications, and death [50–58]. However, current data do not show an increase in the number of patients with CLD, the prevalence of which is 3%, suggesting no increased susceptibility to infection in this population [80–83]. However, patients with CLD may be at higher risk of developing more severe COVID-19 disease and higher mortality compared to patients without CLD. Indeed, a large study of 2,780 COVID-19 patients that compared outcomes among patients with and without CLD reported that patients with CLD had an approximately 3-fold higher mortality risk than patients without CLD, and this risk was significantly higher in patients with CLD and cirrhosis (~5-fold).

Also, complications on the liver after coronavirus are caused by medications: antibiotics, antivirals, antipyretics, hormonal, anti-inflammatory and drugs of other groups used in the treatment of COVID -19. Many of the medications recommended for the treatment of coronavirus have a toxic effect on the liver, thereby causing its damage [54-59].

This fact may occur in patients with COVID-19, when liver failure has not been noted, even in the most severe and fatal cases of the disease. Thus, questions remain, the answers to which will probably be obtained in the future. However, patients with chronic progressive liver diseases of any etiology at the stage of cirrhosis, due to decreased immunity, patients after liver transplantation and, possibly, with autoimmune diseases, are at risk and in some cases require additional measures. Liver injury during the pandemic is a broad spectrum of potential pathomechanisms, including direct cytotoxicity due to active SARS-CoV-2 viral replication in the liver, [80–82] immune-mediated liver injury due to severe inflammatory response/systemic inflammatory response syndrome

(SIRS) in COVID-19, 42 hypoxic changes due to respiratory failure, vascular changes due to coagulopathy, endotheliitis, or cardiac congestion due to right heart failure, drug-induced liver injury, and exacerbation of underlying liver disease [66–68]. Given the central role of the liver in the production of albumin, acute phase reactants, and coagulation factors, liver dysfunction may contribute to the multisystem manifestations of COVID-19, such as ARDS, coagulopathy, and multiple organ failure [52–54]. The possible mechanism for the development of hepatic coagulopathy in coronavirus infection may consist of :

- decreased synthesis of coagulation factors (pathological fibrinogen), impaired synthesis of vitamin K
- thrombocytopenia (hypersplenism with platelet sequestration, decreased thrombopoietin production)
- reduced degradation of activated coagulation factors (DIC syndrome) and increased activation of the fibrinolytic system - hyperfibrinolysis [80].

In SARS-CoV-2 infected hepatocytes, marked mitochondrial swelling, endoplasmic reticulum dilation, and reduction of glycogen granules were observed. Histologically, massive hepatic apoptosis and some binucleated hepatocytes were observed. Collectively, both ultrastructural and histological findings indicated typical damage by viral infection [25-28].

Patients with non-alcoholic fatty liver disease (NAFLD), especially steatohepatitis (NASH) and co-morbid metabolic diseases such as diabetes, hypertension and obesity, have an increased risk of more severe COVID-19 [15-21].

It has been established that the prognosis for the course of COVID-19 worsens in patients with increased ALT activity, decreased platelet count, and decreased albumin levels at the time of hospitalization, which corresponded to the progressive course of liver cirrhosis (Child-Pugh classification). A summary of the treatment results obtained from Oxford University Hospital NHS Foundation Trust and the University of North Carolina revealed an increase in

mortality in patients with liver cirrhosis of up to 40% [21-23]. The presence of decompensated liver cirrhosis naturally increased the undesirable outcome of the disease to 43-63%. Any systemic viral infections can occur with transient increases in transaminase activity, which reflect the development of a systemic inflammatory response caused by circulating cytokines (the so-called “reactive hepatitis”), which will certainly worsen the course of chronic liver diseases [5-8].

Published studies on COVID-19 have shown that 37.2–76.3% of patients have liver dysfunction [12–16]. Similarly, the prevalence of liver injury has been reported to be approximately 21.5–45.71% of patients [23–32]. Overall, 7.14–64.15% of COVID-19 patients had elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and bilirubin, while albumin was decreased to 27.9–33.0 g/L in non-surviving patients. In addition, COVID-19 patients with chronic liver disease (CLD) may develop liver decompensation as a systemic inflammatory response caused by COVID-19 [43–46].

The prevalence of CLD was 4% (95% CI 1.5 to 6.4, I2 = 89%) among COVID-19 patients, with cirrhosis and hepatitis B being the most common. Similarly, the incidence of liver injury was 27% (95% CI 18.2 to 35.8, I2 = 97%; 1) [[68-71]. It should be noted that elderly COVID-19 patients had a higher risk of liver injury (standardized mean difference (SMD): 0.81, 95% CI 0.32 to 1.29, I2 = 85%, p = 0.001).

From the study by Andrew M. et al. included 103 patients with liver cirrhosis and 49 patients with non-cirrhotic CLD, which suggested that for patients with cirrhosis, the rates included intensive care unit (ICU) admission in 23.3%, invasive ventilation in 17.5%, non-invasive ventilation in 18.6%, renal replacement therapy in 4.9%, and death in 39.8% [74-75].

The cause of death in patients with cirrhosis was listed as COVID-19 pulmonary disease in 78.7%, cardiovascular disease in 4.3%, and liver disease in 12.2%. Risk factors for adverse COVID-19 outcomes in the general population,

including older age, obesity, renal failure, heart disease, and diabetes mellitus, were overrepresented among decedents, although male gender and non-white ethnicity were not [79]. Mortality was highly correlated with baseline Child-Pugh class and Model for End-Stage Liver Disease (MELD) score. Death occurred in 12.2% of patients with CLD without cirrhosis, 23.9% with Child-Pugh class A cirrhosis , 43.3% with Child-Pugh class B cirrhosis, and 63.0% with Child-Pugh class C cirrhosis.

Hepatic decompensation occurred in 36.9% and was related to the baseline Child-Pugh class. Events of decompensation included worsening ascites (27.2%), spontaneous bacterial peritonitis (2.9%), hepatic encephalopathy (16.5%), and variceal bleeding (1%). Liver decompensation during COVID-19 was strongly associated with subsequent mortality risk: 63.2% of patients with new decompensation died compared with 26.2% of those without new decompensation. Notably, 24.3% of patients with new liver decompensation did not have respiratory symptoms of COVID-19 at diagnosis [80].

At autopsy of patients with COVID-19, the liver is dark red, enlarged; the gallbladder is large. Microscopic examination reveals microvesicular steatosis, focal necrosis of hepatocytes, predominance of neutrophils in lobular and portal infiltrates, microthrombi in the sinusoids [81]. Meanwhile, the described histological changes may be caused to a greater extent by drug-induced liver injury, rather than SARS - CoV -2 [76-78].

Between 25 March and 8 July 2020, data on 745 patients with CLD and SARS-CoV-2 (including 386 with cirrhosis and 359 without cirrhosis) were collected from two international registries and compared with data on non-CLD patients with SARS-CoV-2 from a UK hospital network.[82]

Mortality was 32% in patients with cirrhosis compared with 8% in patients without cirrhosis ($p < 0.001$). Mortality in patients with cirrhosis increased by Child-Pugh class (A [19%], B [35%], C [51%]), and the main cause of death was respiratory failure (71%). After adjustment for baseline

characteristics, factors associated with death in the overall CLD cohort were age (odds ratio [OR] 1.02; 1.01–1.04), Child-Pugh class A (OR 1.90; 7.65) or C (OR 9.32; 4.80–18.08) cirrhosis, and alcoholic liver disease (OR 1.79; 1.03–3.13). Compared with patients without CLD (n = 620), propensity score-matched analysis revealed a significant increase in mortality in patients with Child-Pugh class B (+20.0% [8.8–31.3%]) and C (+38.1% [27.1–49.2%]) cirrhosis. Acute liver decompensation developed in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms [83].

1.5. Genetic and immunological factors influencing the course of chronic kidney disease after COVID-19

Genetic factors play a significant role in the progression of chronic liver diseases (CLD), especially after COVID-19 infection. One of the key genes associated with non-alcoholic fatty liver disease (NAFLD) is PNPLA3 (patatin lipase-like phospholipase). Polymorphism of this gene (rs738409 C>G variant) is associated with a higher probability of developing steatosis, steatohepatitis and fibrosis progression. Studies show that carriers of the G variant have a 1.5-2-fold increased risk of liver function deterioration after COVID-19. In addition, polymorphisms of genes associated with lipid metabolism, inflammation and immune response (e.g. TM6SF2, MBOAT7) also affect the severity of LDD.

In patients with genetically determined impairment of iron metabolism (e.g., mutations in the HFE gene causing hemochromatosis), COVID-19 may activate iron accumulation in the liver, worsening inflammation and increasing the risk of fibrosis. Genetic mutations associated with antioxidant defense (e.g., mutations in the SOD2 gene) may increase the vulnerability of the liver to oxidative stress caused by hypoxia and inflammation in COVID-19.

Immunological factors also play a key role in the pathogenesis of post-COVID-19 CLD. SARS-CoV-2 infection causes hyperactivation of the immune system, leading to a cytokine storm that has a significant impact on the liver. High levels of proinflammatory cytokines such as IL-6, IL-1β, and TNF-α

enhance inflammatory responses in the liver by activating hepatic stellate cells, which contributes to the progression of fibrosis. In patients with autoimmune liver diseases, including autoimmune hepatitis, COVID-19 may enhance T-regulatory cell dysfunction, leading to increased autoimmune inflammation.

Systemic inflammation caused by COVID-19 can activate immune pathways associated with innate immunity, including Toll-like receptors (TLRs). TLR activation in the liver leads to increased production of reactive oxygen species (ROS), which exacerbates tissue damage. Innate defects in the immune response, such as mutations in the TLR4 or NOD2 genes, increase the risk of microbial translocation and exacerbation of chronic kidney disease after COVID-19.

In addition, in patients with viral hepatitis B or C, COVID-19 may provoke reactivation of the infection by suppressing the activity of cytotoxic T cells and dysfunction of the interferon response. This leads to an increase in the viral load and deterioration of the clinical condition of patients.

The interaction of genetic and immunological factors after COVID-19 creates a high probability of exacerbation of chronic liver disease, acceleration of fibrosis progression and development of complications. Modern approaches to diagnostics and treatment should take into account both the individual genetic characteristics of the patient and the immunological profile in order to minimize risks and ensure effective management of chronic liver diseases.

In addition to known genetic and immunological factors, increasing attention is paid to the interaction between epigenetic modifications and the course of chronic liver diseases (CLD) after COVID-19. Epigenetic changes such as DNA methylation, histone modification, and microRNA (miRNA) regulation play a key role in regulating genes associated with inflammation, fibrosis, and liver regeneration. For example, methylation changes in the promoter regions of genes regulating cytokine expression (IL-6, TNF-α) can enhance the inflammatory response, creating favorable conditions for exacerbation of fibrosis.

MicroRNAs such as miRNA-122 and miRNA-34a are involved in the regulation of lipid metabolism, inflammation, and hepatocyte apoptosis. In patients with chronic liver disease who have had COVID-19, changes in the levels of these molecules are observed, which is associated with accelerated steatosis development, activation of hepatic stellate cells, and increased collagen formation. Studies show that restoring normal microRNA levels may be a promising target for therapeutic intervention.

At the molecular level, COVID-19 activates pathways such as JAK/STAT, MAPK, and NF-κB, which are involved in inflammation and fibrosis. These signaling cascades may be hyperactivated in patients with a genetic predisposition to inflammatory responses. For example, mutations in the SOCS3 gene, which is an inhibitor of the JAK/STAT pathway, may contribute to the continuous activation of inflammation, exacerbating liver injury.

Particular attention should be paid to the role of mitochondrial dysfunction in the pathogenesis of post-COVID-19 LD. The SARS-CoV-2 virus disrupts liver energy metabolism through a direct effect on mitochondria, causing their fragmentation, decreased ATP synthesis, and increased levels of reactive oxygen species (ROS). These changes aggravate hepatocyte apoptosis and activate stellate cells, promoting fibrosis. In patients with mutations in mitochondrial genes or reduced mitochondrial biogenesis, COVID-19 can significantly accelerate the progression of liver diseases.

There is evidence that the gut microbiota plays an important role in modifying the immune response and inflammatory processes in the liver after COVID-19. Dysbiosis caused by the infection and its treatment increases the entry of microbial metabolites, such as lipopolysaccharides (LPS), into the portal venous system. These metabolites activate Kupffer cells via TLR4, promoting the release of proinflammatory cytokines and hepatocyte damage. Genetic variants affecting the composition of the microbiota and intestinal barrier permeability (e.g., mutations in the ZO-1 gene) may increase the sensitivity of the liver to these influences.

It is also relevant to consider the impact of immune senescence on the course of chronic liver disease in elderly patients who have had COVID-19. With age, the immune system loses the ability to effectively regulate inflammation, which leads to chronic activation of the low-level inflammatory process (inflammaging). In elderly patients with pre-existing liver disease, this chronic activation, supplemented by the impact of COVID-19, accelerates the progression of fibrosis and the development of complications.

Promising studies are also looking at the contribution of autophagy to liver protection. COVID-19 suppresses autophagy, which impairs the clearance of damaged organelles and proteins in hepatocytes. This contributes to the accumulation of cellular stress and increases inflammation. Genetic polymorphisms in autophagy-related genes (e.g., ATG5 and LC3) may amplify this effect, creating conditions for the rapid progression of CDLD.

These profound molecular and systemic aspects of the pathogenesis of post-COVID-19 CDD highlight the need to develop personalized treatment strategies based on the genetic and immunological profiles of patients. They also open new perspectives for the use of targeted therapies aimed at regulating epigenetic changes, microbiota, mitochondrial function, and autophagy.

In addition to the molecular and systemic factors mentioned above, an important area of study remains the interaction of the SARS-CoV-2 virus with cellular signaling pathways that control inflammation, regeneration, and immune tolerance in the liver. For example, activation of the Wnt/β-catenin signaling pathway, which is important for liver regeneration, may be disrupted in COVID-19, especially in patients with pre-existing chronic diseases. This imbalance reduces the liver's ability to recover and creates conditions for the progression of fibrosis.

Another important aspect is the role of redox processes. COVID-19 causes dysregulation of antioxidant systems such as glutathione and superoxide dismutase, which leads to increased oxidative stress. Genetic variations in genes encoding antioxidant enzymes (e.g., GSS, SOD1) may determine individual

liver sensitivity to oxidative damage. Patients with impaired antioxidant defense are more likely to experience accelerated development of steatosis, inflammation, and fibrosis.

In recent years, increasing attention has been paid to the role of exosomes in the pathogenesis of liver diseases. SARS-CoV-2 alters the composition and function of exosomes secreted by liver cells and the immune system. These extracellular vesicles carry proinflammatory molecules such as IL-6 and TNF-α, enhancing intercellular inflammatory signals. In patients with CDLD, this mechanism may contribute to the spread of inflammation and hepatocyte damage. The study of exosomes as a possible therapeutic target is a promising direction for preventing the progression of liver diseases.

Additionally, the impact of COVID-19-induced metabolic adaptations on the course of CLD should be considered. The virus alters cellular energy metabolism, switching it from aerobic to anaerobic glycolysis. This metabolic shift promotes lactate accumulation and reactive oxygen species production, which increases inflammation and fibrosis. In patients with pre-existing disorders of lipid or carbohydrate metabolism, such as NAFLD or diabetes mellitus, these changes may worsen the course of the disease. Genetic factors regulating metabolism (e.g., PPARγ gene variants) also play a significant role in the liver's adaptive responses.

Particular attention should be paid to the influence of neurohumoral mechanisms. COVID-19 activates the hypothalamic-pituitary-adrenal axis, which leads to chronic hypercortisolemia. In patients with chronic hepatic dysfunction, this can increase catabolic processes, reduce the regenerative capacity of the liver, and aggravate inflammation. Moreover, chronic stress caused by the pandemic contributes to an increase in cortisol levels, which further increases the dysfunction of the immune system and liver.

In terms of treatment prospects, therapy aimed at restoring liver immune tolerance is of particular importance. The use of regulatory T cells (Tregs) or drugs that stimulate their activity can help reduce autoimmune inflammation and

maintain homeostasis. The possibility of using drugs that modulate the interaction between the microbiota and the immune system, such as prebiotics, probiotics, and postbiotics, is also being considered. These substances are able to restore the balance of the microbiota and reduce the penetration of inflammatory metabolites into the portal vein.

Finally, studying the role of rare genetic syndromes such as Wilson disease or alpha-1 antitrypsin syndrome in the context of COVID-19 and CDLD may shed light on new treatment targets. These conditions are exacerbated by viral infection, requiring an individualized approach to diagnosis and therapy. Combined analysis of genetic data, epigenetic changes, and clinical features of patients provides the basis for personalized medicine, which is becoming a key tool in the management of CDLD after COVID-19.

In addition to known mechanisms, there is growing evidence that dysfunction of the endothelial system plays a central role in the exacerbation of chronic liver disease (CLD) after COVID-19. SARS-CoV-2 causes endothelial cell injury through direct viral exposure and activation of inflammatory mediators. Disruption of the endothelial barrier in the liver sinusoids promotes the development of microthrombosis and hypoxia, which aggravates ischemic injury to hepatocytes. Patients with genetic variations in genes regulating endothelial function, such as NOS3 or VEGF, may be particularly susceptible to these changes, posing additional risks for fibrosis progression.

The role of vascular dysfunction is enhanced by the presence of concomitant metabolic diseases such as dyslipidemia and hypertension, which themselves contribute to endothelial damage. In these circumstances, COVID-19 becomes a catalyst for the deterioration of microcirculation, especially in patients with pre-existing portal hypertension syndrome. This raises the question of the appropriateness of using anticoagulants in post-COVID therapy of patients with CDLD in order to minimize the risk of thrombosis without increasing the risk of bleeding.

An interesting area is the effect of chronic systemic inflammation on the liver extracellular matrix. Patients with COVID-19 show significant activation of matrix metalloproteinases (MMPs), which play a key role in tissue matrix remodeling. These enzymes, by regulating the balance between collagen synthesis and degradation, affect the progression of fibrosis. Genetic polymorphisms in the MMP2 and MMP9 genes can enhance the activity of these enzymes, which leads to more rapid formation of the pathological collagen framework in the liver. This opens up opportunities for the development of targeted drugs that suppress excess MMP activity.

Additionally, changes in lipid metabolism caused by SARS-CoV-2 and their role in the development of steatosis and steatohepatitis should be taken into account. The virus alters the function of key lipogenesis enzymes, such as SREBP-1c, which promotes the accumulation of triglycerides in hepatocytes. Patients with pre-existing lipid metabolism disorders, for example due to genetic variants of the FADS1 gene, are more likely to develop steatohepatitis after COVID-19. This underlines the importance of metabolic therapy aimed at reducing insulin resistance and restoring lipid balance.

Psychoneuroimmunology is becoming another important area of study. Chronic stress caused by the pandemic and its aftermath affects liver function through a complex interaction between the nervous and immune systems. Activation of the sympathetic nervous system and the release of stress hormones such as adrenaline and cortisol contribute to the activation of hepatic stellate cells and increased inflammation. Moreover, stress contributes to changes in the composition of the gut microbiota, which in turn increases the permeability of the intestinal barrier and enhances the penetration of lipopolysaccharides (LPS) into the blood. This process aggravates liver inflammation and can accelerate fibrosis.

Additionally, the influence of epigenetic legacies, which can be transmitted across generations and increase susceptibility to exacerbations of CDLD, should be considered. For example, chronic stress, exposure to toxins, or

nutritional deficiencies can cause persistent changes in gene expression through histone modification or DNA methylation. These epigenetic changes may be amplified by COVID-19, increasing the risk of liver disease progression in offspring.

Innovative treatment approaches, such as the use of circulating biomarkers to predict outcomes, may also play a significant role. For example, studying the expression of fibrosis-associated microRNAs (e.g. miRNA-21 or miRNA-29) may enable prediction of disease progression at early stages. Personalized therapy based on these data is becoming an integral part of future strategies for the management of CDLD.

Overall, a better understanding of the interactions between genetic, immunological, epigenetic and metabolic factors after COVID-19 opens up new horizons in the diagnosis, treatment and prevention of exacerbations of chronic liver disease. This area requires further research and the development of targeted approaches that can minimize the long-term consequences of COVID-19 for patients with chronic liver disease.

As we continue our research, we will delve deeper into the impact of intercellular communication via exosomes and extracellular vesicles, which play a key role in modulating liver inflammation and fibrosis after COVID-19. Exosomes secreted by SARS-CoV-2-infected cells contain viral RNA, proinflammatory cytokines, and proteins that can stimulate immune cells and activate hepatic stellate cells. This creates a cascade of inflammatory processes that enhance fibrosis. Studies show that specific changes in the composition of exosomes, including the presence of miRNA-155 and other proinflammatory molecules, are associated with fibrosis progression. Targeting exosomes or their composition may be an innovative approach to the treatment of chronic liver disease.

Another interesting aspect is the impact of liver-microbiota axis disturbances on the immune response and inflammation after COVID-19. SARS-CoV-2 infection causes significant changes in the gut microbiota

composition, including a decrease in beneficial bacteria such as Lactobacillus and Bifidobacterium and an increase in opportunistic bacteria producing lipopolysaccharides (LPS). These LPS increase inflammation via the activation of TLR4 receptors in the liver, which contributes to the development of fibrosis. Genetic predispositions to dysbiosis, such as variations in the FUT2 or NOD2 genes, may enhance this effect, increasing the risk of exacerbation of CDH. Therapeutic probiotics, prebiotics and postbiotics can partially restore the liver-microbiota axis and reduce inflammation.

Another important area of research is the role of mitochondrial DNA (mtDNA) as immunomodulators. Patients with COVID-19 have increased release of mtDNA into the systemic circulation due to mitochondrial damage. These molecules are perceived as “danger signals” and activate the innate immune system, increasing inflammation through pathways such as cGAS-STING. In patients with CDK, who already have elevated levels of mitochondrial stress, the release of mtDNA may exacerbate inflammation and accelerate disease progression. Therapeutic approaches aimed at restoring mitochondrial function, such as the use of mitochondrial antioxidants (e.g., mitokinones), represent a promising direction.

The immune system also undergoes long-term changes after COVID-19, which may influence the course of CDD. For example, SARS-CoV-2 causes exhaustion and dysfunction of T cells, including CD8+ and CD4+ lymphocytes, which play a key role in antiviral immunity and inflammation regulation. In patients with CDD, this exhaustion worsens the course of the disease, increasing the risk of infectious complications and viral reactivations, such as hepatitis B reactivation. Approaches to restore T cell immunity, such as the use of immunomodulators or cell-based therapies, may be useful in such cases.

An important area of study is the impact of long-term COVID-19-induced hypoxia on hepatic stellate cells (HSCs). Chronic hypoxia activates HSCs, which transform into myofibroblasts and produce large amounts of collagen, which accelerates fibrosis. Hypoxia also activates HIF-1α pathways, which

enhance angiogenesis and inflammation, creating a favorable environment for the progression of cirrhosis. Inhibitors of HIF-1α or its regulators are considered as potential therapeutic targets.

New data also suggest that SARS-CoV-2 may affect the expression of genes associated with cell cycle regulation and apoptosis in hepatocytes. This may lead to the accumulation of senescent cells, which, despite stopping cell division, actively secrete proinflammatory cytokines, increasing inflammation and tissue damage. Removal of senescent cells using senolytics is a new direction that is actively being explored in the context of liver diseases.

Additionally, it is worth considering the impact of dysregulation of bile formation and bile flow after COVID-19. Dysregulation of proteins such as BSEP and MRP2 responsible for bile acid transport may lead to their accumulation in the liver, causing inflammation and cholestatic stress. These changes may be enhanced by genetic predisposition, such as mutations in the ABCB11 or ABCG5/8 genes. The use of drugs regulating bile acid transport, such as ursodeoxycholic acid, may be useful in such cases.

These lines of research highlight the complexity of interactions between genetic, epigenetic, immunological and metabolic mechanisms that influence post-COVID-19 LD. Understanding these processes provides the basis for developing new, more effective approaches to diagnosis, treatment and prevention of liver disease progression.

Conclusion to Chapter I

In recent months, several studies have identified a potential role for liver involvement in COVID-19 infection and pathology.

Elevated liver enzymes reflecting liver injury are common in COVID-19 patients with and without chronic liver disease [80]. Interestingly, while early clinical studies found significant elevations in serum ALT and AST exclusively in SARS-CoV-2 infection, reflecting hepatocellular injury, recent studies and meta-analyses have also found significant elevations in ALP and γ- GT and hence cholangiocellular injury [72]. However, it is still unclear whether elevated serum liver biochemistry markers are a cause of worse outcome or a consequence of severe disease.

In COVID-19 patients without pre-existing liver disease who experience liver injury, the injury is generally mild. However, given the central role of the liver in endo- and xenobiotic/drug metabolism , coagulation, albumin production, and acute phase reactants, liver dysfunction may influence the pathophysiology of systemic disease in COVID-19. Long-term follow-up studies are needed to examine potential long-term sequelae of SARS-CoV-2 infection, such as fibrosis.

The establishment of international registries collecting clinical reports of patients with liver disease who also tested positive for COVID-19, such as COVID-Hep and SECURE-Cirrosis, [54–58] together with molecular and translational research will undoubtedly help us shed light on these issues . and intriguing questions and create more effective hepatoprotective programs for future pandemics.

SARS-CoV-2 infection in the liver directly contributes to liver failure in COVID-19 patients. Therefore, monitoring of viral clearance in the liver and long-term outcome of COVID-19 is required.

CHAPTER II. PATHOGENESIS, IMMUNOLOGICAL AND BIOCHEMICAL ASPECTS OF THE IMPACT OF COVID-19 ON THE LIVER

2.1. Effect of SARS-CoV-2 on liver function

1. Direct action of the virus through ACE2 receptors

The SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2), which is expressed in liver cells, including cholangiocytes (60% of ACE2 expression). The virus enters the cells through receptor-mediated endocytosis, which causes cell destruction and functional failure.

- **Damage mechanism:**
  - Direct damage to hepatocytes.
  - Disruption of bile-forming function due to damage to cholangiocytes.
  - Initiation of the inflammatory process through activation of Toll-like receptors (TLRs) in response to viral components.
- **Development:**
  - Apoptosis and necrosis of hepatocytes.
  - Violation of bile outflow, which contributes to the development of cholestasis.
  - Progression of inflammation, which can become chronic .

2. Immune-mediated liver damage

- The immune system responds to SARS-CoV-2 by hyperactivating innate and adaptive immunity. This leads to the formation of a cytokine storm that damages the liver.

- **Mechanism:**
  - High levels of IL-6, TNF-α, and IL-1β trigger a cascade of inflammatory reactions.
  - Activation of Kupffer cells and migration of T lymphocytes to the liver causes tissue damage through cytokine secretion and oxidative stress.
- **Development:**

- Inflammatory infiltrates in the portal zones of the liver.
- Development of microthrombosis and ischemia.
- Increased risk of chronic inflammation and fibrosis.

3. Hypoxia and the influence of cytokine storm

- **Pathogenesis:** Hypoxia caused by impaired blood oxygenation in severe pneumonia and acute respiratory distress syndrome (ARDS) causes hypoxic-ischemic liver injury.
- **Mechanism:**
  - Decreased blood supply to the liver due to microthrombosis.
  - Activation of the hepatocellular apoptotic program due to hypoxia.
- **Development:**
  - Hepatocyte necrosis in the centrilobular zones (zone III of the acinus).
  - Progression of liver steatosis and fibrosis.

4. The role of hypoxic-ischemic liver damage in the development of chronic complications

- **Pathogenesis:** Chronic hypoxia and oxidative stress cause permanent damage to the mitochondria of hepatocytes, which disrupts energy metabolism.
- **Mechanism:**
  - Increased production of reactive oxygen species (ROS).
  - Decreased synthesis of ATP, which is necessary for cell regeneration.
- **Development:**
  - Accelerated development of steatosis, steatohepatitis.
  - Progression to cirrhosis and development of liver failure.

2.2. Immune response and cytokine storm

1. The role of inflammatory cytokines (IL-6, IL-1β, TNF-α) in liver damage

1. IL-6 and its role in liver damage

- **Pathogenesis:** IL-6 is one of the key pro-inflammatory cytokines produced by macrophages, T cells, and Kupffer cells (resident liver

macrophages). It is activated in response to an infectious agent, in this case SARS-CoV-2, which leads to the initiation of a systemic inflammatory response.

- ***Mechanism of action:***
  - IL-6 binds to the IL-6 receptor (IL-6R), forming a complex that interacts with the gp130 protein, activating the JAK/STAT signaling pathway.
  - Activation of this pathway stimulates the expression of genes responsible for inflammation, antiapoptosis, proliferation and acute phase response in the liver.
- ***Development of liver damage:***
  - Elevated IL-6 levels induce the synthesis of acute phase proteins such as C-reactive protein and fibrinogen, which may contribute to hypercoagulability and microthrombosis in the liver.
  - Increased inflammatory response in the liver leads to damage to hepatocytes, the development of steatosis and stimulates fibrogenesis processes due to the activation of hepatic stellate cells.
  - Chronic activation of IL-6 is associated with increased fibrosis processes and may accelerate the transition to cirrhosis.

2. IL-1β and its role in liver damage

- **Pathogenesis:** IL-1β is a key mediator of the inflammatory cascade activated by the inflammasome (NLRP3 inflammasome). In COVID-19, inflammasome activation occurs in response to viral antigen, tissue damage, and the formation of reactive oxygen species (ROS).
- ***Mechanism of action:***
  - IL-1β activates endothelial cells, enhancing the expression of adhesion molecules (ICAM-1, VCAM-1), which promotes the migration of leukocytes to the liver.
  - Activates Kupffer cells, increasing their production of cytokines and free radicals, which worsens liver tissue damage.
  - Enhances hepatocyte apoptosis through caspase activation and mitochondrial damage.

- ***Development of liver damage:***

  - In the liver, IL-1β causes increased vascular permeability, leading to edema and inflammation.
  - Chronic exposure to IL-1β promotes activation of hepatic stellate cells, which stimulates excessive collagen deposition and the development of fibrosis.
  - Damage to the vascular endothelium increases hypoxia, which leads to ischemic damage to hepatocytes.

3. TNF-α and its pathogenetic role

- **Pathogenesis:** TNF-α (tumor necrosis factor alpha) is a central inflammatory mediator produced by macrophages, Kupffer cells, and neutrophils in response to SARS-CoV-2 infection.
- ***Mechanism of action:***
  - TNF-α interacts with two types of receptors: TNFR1 and TNFR2.
  - TNFR1 initiates the NF-κB cascade, which activates inflammatory genes, increasing the secretion of proinflammatory mediators and chemokines.
  - TNFR1 activates apoptotic pathways, including caspases, leading to hepatocyte death.
  - TNF-α increases oxidative stress, causing mitochondrial dysfunction and ROS production.
- **Development of liver damage:**
  - TNF-α induces apoptosis and necrosis of hepatocytes.
  - Enhances activation of hepatic stellate cells, leading to fibrosis and tissue remodeling.
  - Causes disruption of microcirculation in the liver, contributing to ischemic changes.

The importance of hyperactivation of the immune system and the formation of systemic inflammation syndrome

- **Pathogenesis:** Systemic inflammatory syndrome (SIRS) develops due to excessive activation of the immune system against the background of

COVID-19. The basis of pathogenesis is the uncontrolled release of proinflammatory cytokines, which leads to damage to tissues and organs.

- **Mechanisms of liver damage:**

1. **Endothelial damage:**

Proinflammatory cytokines damage endothelial cells, increasing vascular permeability and causing tissue ischemia.

2. **Thrombosis:**

Activation of the blood coagulation system leads to microthrombosis in the liver, aggravating ischemic damage.

3. **Oxidative stress:**

Increased formation of free radicals leads to damage to lipids, proteins and DNA of hepatocytes.

- **Development of complications:**
  - Worsening of liver fibrosis.
  - Risk of progression to cirrhosis.
  - Increased risk of multiple organ failure.

2.3. Biochemical and metabolic disorders

Major biochemical changes

1. Violation of the enzyme profile

- Increased levels **of alanine aminotransferase (ALT)** and **aspartate aminotransferase (AST)** :
  - Indicates damage to hepatocytes.
  - AST > ALT is often associated with hypoxic liver injury.
- Increased **gamma-glutamyl transferase (GGT)** and **alkaline phosphatase (ALP)** :
  - Typical for cholestatic lesions caused by impaired bile formation.
- **Hyperbilirubinemia** :
  - May result from hepatocyte damage or cholestasis.
  - Total bilirubin levels correlate with COVID-19 severity.

Statistics :

- In 15–30% of patients with COVID-19, elevated ALT and AST are observed, and in 10–20%, hyperbilirubinemia.

2. Coagulopathy

- Decreased albumin levels :
  - Indicates a disturbance of the liver's synthetic function and is often observed in severe patients.
  - Low albumin is associated with increased mortality.
- Increased prothrombin time (PT) **and** international normalized ratio (INR) **:**
  - Indicates a decrease in the liver's ability to synthesize clotting factors.
  - Elevated D-dimer levels are associated with thrombotic complications.

Metabolic disorders

1. Disorders of lipid metabolism

- Increased levels of **free fatty acids (FFAs)** and **triglycerides** in blood plasma:
  - Activation of lipolysis during systemic inflammation leads to accumulation of fats in the liver (steatosis).
- Increased **lipotoxicity** :
  - Excess fatty acids cause oxidative stress, damage mitochondria and activate hepatocyte apoptosis.

Mechanism of action :

- Fat droplets in hepatocytes disrupt their functions, increase inflammation and provoke fibrosis.

2. Disruption of carbohydrate metabolism

- Insulin resistance:
  - COVID-19 increases tissue insulin resistance through increased levels of proinflammatory cytokines.
  - Decreased glucose utilization leads to hyperglycemia.
- Increased **glucose levels** :

- Hyperglycemia increases oxidative stress and inflammation in the liver.

Statistics :

- In 20–40% of patients with COVID-19, especially those with concomitant diabetes, carbohydrate metabolism disorders are observed.

3. Violation of amino acid metabolism

- Decreased levels of **branched chain amino acids (BCAA)** :
  - Decreased protein synthesis is associated with weakened liver function.
- Increased levels of **aromatic amino acids (AAA)** :
  - A decrease in their metabolism indicates the initial signs of hepatic encephalopathy.

The effect of hypoxia on liver metabolism

Hypoxic mechanism :

- Impaired oxygen delivery to the liver in severe COVID-19 leads to ischemic cell damage.
- Hypoxia causes:
  - Mitochondrial dysfunction.
  - Transition to anaerobic metabolism.
  - Increased lactate (lactic acidosis).

Results :

- Acidosis disrupts the functioning of the liver's enzymatic systems and increases hepatocyte necrosis.

Cytokine storm and its metabolic consequences

Pathogenesis :

- High levels of IL-6 and TNF-α activate transcription factors (NF-κB), which enhance inflammation and apoptosis.
- Decreased expression of insulin receptors and impaired mitochondrial function lead to systemic metabolic disorders.

Biochemical and metabolic liver abnormalities in COVID-19 develop due to a complex interaction between direct viral exposure, hypoxia, systemic inflammation, and drug-induced injury. These changes are exacerbated by

metabolic syndromes and underlying liver diseases.

2.4. The role of associated factors

Liver injury in patients with COVID-19 is a complex and multifactorial phenomenon. In addition to the direct impact of the SARS-CoV-2 virus, comorbid factors such as chronic liver diseases, metabolic disorders, drug-induced hepatotoxicity, and others play a key role in the development of pathology. They can increase inflammatory and metabolic changes, contribute to liver dysfunction, and worsen disease outcomes.

1. Chronic liver diseases

1.1. Fatty liver disease (NAFLD and NASH)

Pathogenesis :

- Fatty liver disease is characterized by the accumulation of lipids in hepatocytes, causing chronic inflammation and progressive fibrosis. Patients with NAFLD have higher expression of ACE2, which is the pathway through which the SARS-CoV-2 virus enters cells, making the liver more vulnerable to viral damage.
- Systemic inflammation associated with obesity and metabolic syndrome enhances the cytokine storm in COVID-19.

Statistics :

- 25–30% of patients with COVID-19 show signs of fatty liver disease.
- NAFLD increases the risk of severe COVID-19 by 1.5 times, and mortality with a combination of COVID-19 and NASH increases by 40%.

Features of treatment :

- Control of glucose and lipid levels, use of hepatoprotectors and antioxidants.

1.2. Liver cirrhosis

Pathogenesis :

- In cirrhosis, the function of immune cells is impaired, which weakens antiviral immunity.

- Portal vein hypertension contributes to microcirculation disorders and hypoxic liver damage.
- Patients with decompensated cirrhosis have an increased risk of septic shock and multiple organ failure.

Statistics :

- The mortality rate for COVID-19 in patients with cirrhosis is 32–40%, while in patients without cirrhosis it is less than 10%.
- Patients with cirrhosis are 2 times more likely to develop hepatic encephalopathy in the context of COVID-19.

Features of treatment :

- Monitoring liver function, avoiding hepatotoxic drugs, correction of hypoxic conditions.

1.3. Viral hepatitis (HBV and HCV)

Pathogenesis :

- Chronic viral hepatitis increases systemic inflammation and activates cytokines, which worsens liver damage in COVID-19.
- The risk of HBV reactivation is increased by the use of immunomodulators (eg, tocilizumab or glucocorticoids).

Statistics :

- In 10–15% of patients with COVID-19 infected with HBV or HCV, exacerbations of viral infection are observed.
- Patients with HBV have a 20–30% higher mortality rate from COVID-19 compared to the general population.

Features of treatment :

- Antiviral therapy (entecavir, tenofovir), prevention of HBV reactivation.

*2. **Metabolic disorders***

2.1. Diabetes mellitus type 2

Pathogenesis :

- Hyperglycemia enhances the inflammatory response through increased activity of proinflammatory cytokines (IL-6, TNF-α).
- Disruption of microcirculation leads to hypoxic and ischemic liver damage.
- Diabetes exacerbates oxidative stress in hepatocytes.

Statistics :

- Patients with diabetes mellitus have a 2-3 times higher risk of severe COVID-19.
- Increased ALT/AST in patients with diabetes is observed in 45% of cases.

Features of treatment :

- Glucose level control, use of antioxidants and hepatoprotectors.

2.2. Obesity

Pathogenesis :

- Increased fat mass contributes to chronic inflammation and impaired lipid metabolism in the liver.
- High levels of circulating fatty acids and proinflammatory cytokines enhance liver damage.

Statistics :

- Obesity occurs in 35–50% of patients with severe COVID-19.
- Liver damage is reported in 60% of obese patients with COVID-19.

Features of treatment :

- Diet, physical activity, metformin to control metabolic status.

3. ***Drug-induced hepatotoxicity***

Pathogenesis :

- The use of antiviral drugs (remdesivir, lopinavir/ritonavir), immunomodulators (tocilizumab) and antibiotics can cause direct toxic damage to hepatocytes.
- Hepatotoxicity is enhanced in patients with pre-existing liver disease.

Statistics :

- Drug-induced liver injury occurs in 20–25% of patients treated for COVID-19.
- Elevated transaminases are observed in 10–15% of cases when using remdesivir.

Features of treatment :

- Limitation of hepatotoxic drugs, use of hepatoprotectors.

4. Hypoxia and sepsis

4.1. Hypoxia

Pathogenesis :

- Severe hypoxia in COVID-19 causes ischemic liver injury, especially in the acinar areas.
- Hypoxia increases the production of free radicals, leading to oxidative stress.

Statistics :

- Hypoxic liver injury is observed in 50% of patients with respiratory failure due to COVID-19.

Features of treatment :

- Maintaining adequate oxygenation, using antioxidants.

4.2. Sepsis

Pathogenesis :

- Systemic inflammation in sepsis leads to multiple organ failure, including liver failure .
- Microcirculation disorders and thrombosis increase ischemic damage.

Statistics :

- Sepsis is associated with increased mortality in 30–50% of patients with COVID-19 and liver damage.

Features of treatment :

- Antibiotic therapy, liver function support.

5. ***Immunological factors***

Pathogenesis :

- The "cytokine storm" caused by hyperactivation of the immune system leads to a massive release of IL-6, TNF-α and other mediators.
- Autoimmune reactions can trigger the development of autoimmune hepatitis.

Statistics :

- Cytokine storm is recorded in 10–15% of patients with severe COVID-19.
- Autoimmune hepatitis develops in 2–5% of cases.

Features of treatment :

- Immunomodulators (glucocorticoids, IL-6 inhibitors).

Co-morbid factors significantly affect the severity of liver damage in COVID-19. Patients with chronic liver disease, metabolic disorders, obesity, and diabetes are at risk. To improve the prognosis, it is necessary to perform early diagnosis of liver damage, minimize hepatotoxic effects, and adjust treatment taking into account comorbid conditions.

Conclusion to Chapter II

The analysis showed that the SARS-CoV-2 virus has both a direct damaging effect on liver cells through ACE2 receptors and causes indirect disorders due to hypoxia, activation of the immune system and systemic inflammation. Direct damage to cells such as hepatocytes and cholangiocytes is associated with endocytosis of the virus, impaired bile formation and activation of inflammatory processes. These changes lead to necrosis and apoptosis of liver cells, progressive cholestasis and the development of chronic inflammation, which creates the basis for the formation of severe complications.

One of the key mechanisms of liver damage in COVID-19 is the hyperactivation of the immune system, manifested as a cytokine storm. The release of proinflammatory mediators such as IL-6, IL-1β and TNF-α contributes to increased inflammatory reactions, endothelial damage and the formation of microthromboses, which further aggravate ischemic tissue damage. Chronic activation of inflammatory processes increases the risk of fibrosis and cirrhosis, which emphasizes the importance of monitoring the cytokine profile and timely anti-inflammatory therapy.

Additionally, attention is focused on biochemical and metabolic disorders, including changes in the liver enzyme profile, hyperbilirubinemia, coagulopathy, and imbalance in carbohydrate, lipid, and amino acid metabolism. These processes are a consequence of both hypoxic-ischemic changes and systemic inflammation. Hypoxia caused by severe respiratory failure leads to mitochondrial dysfunction, increased production of reactive oxygen species, and disruption of energy metabolism, which further increases liver damage. The interaction between hypoxia and inflammation creates a vicious circle that contributes to the accelerated progression of pathological changes.

An equally important aspect is the influence of comorbid factors such as chronic liver disease, obesity, diabetes mellitus, and drug- induced hepatotoxicity. These conditions aggravate the course of COVID-19 and

increase the risk of adverse outcomes by increasing inflammation, oxidative stress, and metabolic disturbances.

The importance of an integrated approach to the study and treatment of liver damage in patients with COVID-19. The presented data deepen the understanding of pathogenetic mechanisms and highlight the role of early diagnosis, prevention and targeted therapy in improving treatment outcomes.

CHAPTER III. RESULTS OF SCIENTIFIC RESEARCH

3.1. Evaluation of laboratory parameters of patients with chronic pulmonary disease against the background of previous COVID – 19.

Evaluation of laboratory parameters in patients with chronic diffuse liver diseases (CDLD) in the context of COVID-19 is an important component of the diagnosis and management of these conditions. The following are key laboratory parameters that were subject to changes in patients in these groups:

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST):

The levels of these enzymes in patients before COVID-19 infection were within the normal range and above normal values (ALT (M: 42 IU/L; F: 32 IU/L, and AST M : 37 IU/L; F: 31 IU/L)). After infection, an excess of 13.7% of normal values was observed, while ALT reached an excess of 23.5% of normal values regardless of gender, and AST exceeded 18.9% regardless of gender and age. After COVID -19, patients with CDZD developed various concomitant pathological aspects, which also led to an increase in ALT and AST levels.

Bilirubin:

Elevated levels of total bilirubin indicate impaired liver and biliary tract function. The deviation from normal total bilirubin values (1.1-18.8 μmol/l) exceeded 23.6%. In men, the values were exceeded by 27.6%, and in women by 19.2% , which on average indicated an increase of 22.3% . The increase in indirect and direct bilirubin values did not make a definite difference between the sexes and amounted to 22.4%.

Albumen:

The albumin level is an indicator of the functional state of the liver. Thus , from the normal albumin level (38-51 g/l), the decrease was within 15.2% in both sexes.

Prothrombin time (PT) and International Normalized Ratio (INR).

Changes in PT and INR reflect disturbances in the blood clotting system, which is often observed in liver failure. All these factors led to an increase in blood clotting time from normal norms (PT - 11-17 sec, INR - 1.0-1.1) by 8.6%.

Total protein (normally 66-87 g/l) in the female sex, in men there was a significant decrease in its blood. The percentage of decrease from the norm was 13.5%.

Inflammatory markers (C-reactive protein, Leukocytes):

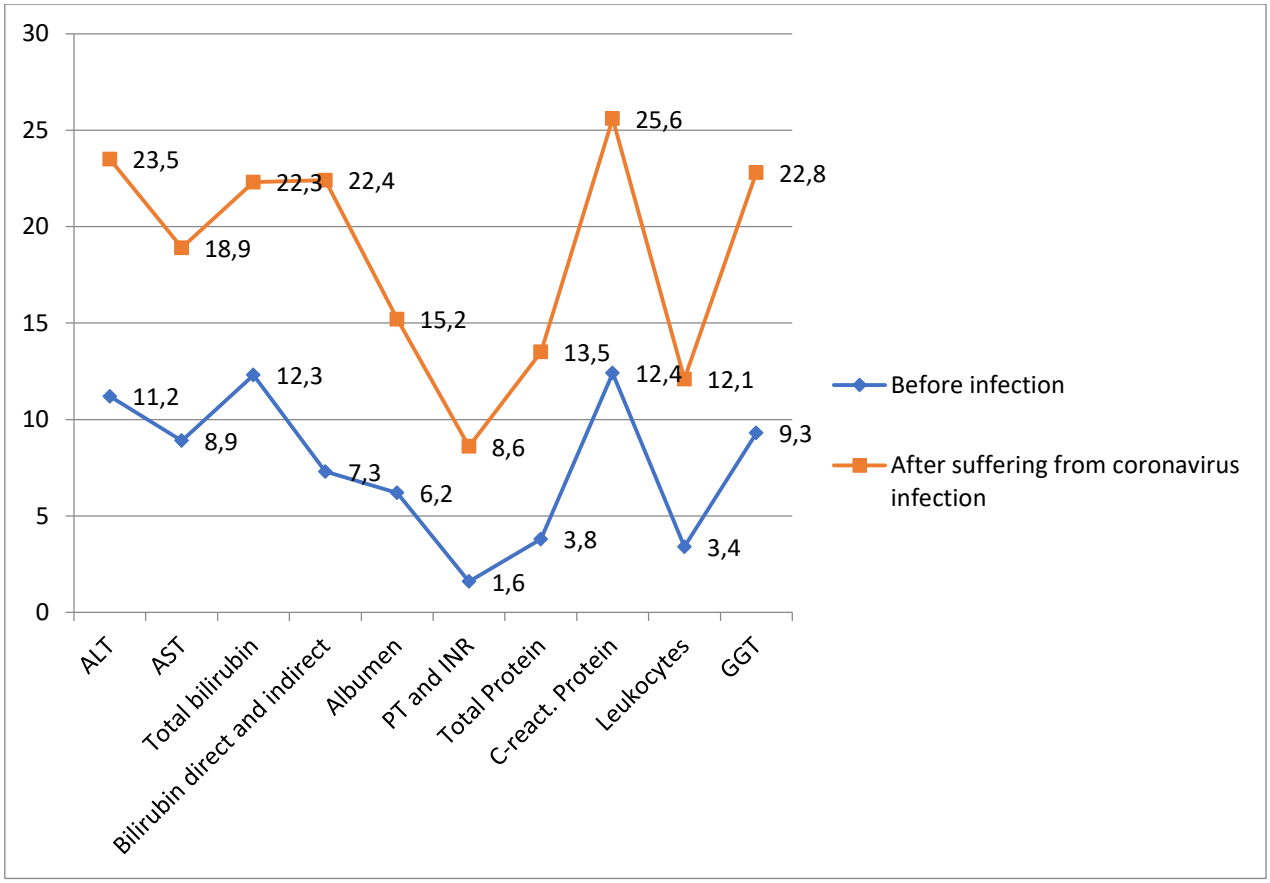
Elevated levels of inflammation markers may indicate the presence of inflammatory processes, including those associated with COVID-19. In most patients, leukocytes (normal 4.0-9.0*109 /l) were elevated above the normal level by 12.1% and amounted to 10.6-9.0*109 /l on average. C-reactive protein was elevated in all patients in both groups. The percentage of the norm was 25.6%.

Aminotransferases:

An excess of aminotransferase activity over the upper limit of the norm by 1.2-3.0 times was considered moderate hyperfermentemia, by 3.1-10 times - moderate, hyperfermentemia by 10.1 or more - high hyperfermentemia (A.I. Khazanov, 1997) .

In addition to ALT and AST, levels of other aminotransferases such as ***gamma-glutamyltransferase*** (GGT) were also assessed. for a more complete analysis of liver function (for men, the norm is up to 11-61 U /l; for women, up to 9-39 U/l). An increase of 15.8% was noted in women, and in men with concomitant diseases of the biliary system, the level of increase was significantly high and amounted to 34.6% , which on average for both sexes was 22.8% (diagram 3.1).

Diagram 3.1. **Levels of increase in tests before/after coronavirus infection**



Grade enzyme immunoassay (ELISA).

Viral markers (Anti - HAV , HBsAg, anti-HCV, Anti-HDV IgM).

Blood tests were taken from 42 patients to detect hepatitis titers. In 14 patients, *HBsAg titers were increased* (normal 0.148) by 18.3%, in 13 patients, an increase in *anti-HCV titers* (0.252) by 26.3%, hepatitis D *Anti-HDV IgM* (0.657) was detected in 8 patients and was an increase from the norm by 13.7%. In 7 patients, a combination of hepatitis B + C, A + C, B + D was detected and the increase in their titers was 26.8% (diagram 3.2).

For patients with chronic liver disease who have had COVID-19, it is important to monitor viral markers to monitor liver function and rule out the influence of viruses on chronic disease.

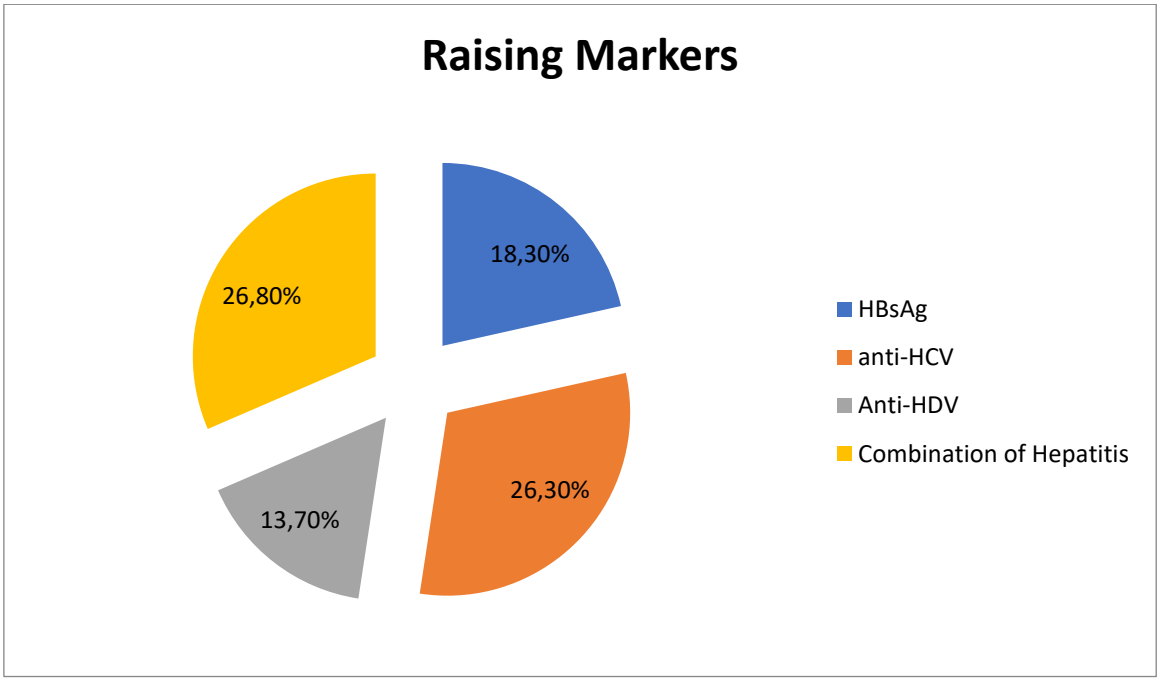


Diagram 3.2. **Increased Hepatitis Markers After COVID-19**

Evaluation of polymerase chain reaction (PCR)

Real-time (quantitative) PCR allows to determine the amount of viral DNA or RNA in a sample, which is useful for assessing the degree of viral load. Detection of hepatitis B virus (HBV) and C (HCV) "normally" may mean the absence of viral DNA (or RNA) in the analyzed sample 0 IU / ml. But since groups with chronic diffuse diseases were studied, their titers ranged from 150,000 IU / ml to 23,000 IU / ml. PCR was performed in 40 patients and the variability of the numbers was different. A significant increase in the virus content was noted after COVID-19 than before the disease. The variability ranged from 254,000 IU / ml and reached 472,000 IU / ml. PCR assessment in patients with chronic diffuse liver diseases in the context of COVID-19 helps in individualizing treatment, determining the degree of inflammation activity and monitoring the patient's condition. These aspects provide medical staff with valuable information for developing an optimal disease management strategy and comprehensive management of the patient with this pathology.

3.2. Results of changes in diagnostic indications of patients with chronic respiratory disease before/after COVID -19 infection.

Ultrasound sonography. Ultrasound was performed in all 60 patients. It was noted that before infection with COVID -19, the echocardiography of the biliary and portal systems and the condition of the liver with spleen were satisfactory in individuals suffering from chronic diffuse liver diseases. After infection, the liver size in patients with chronic hepatitis increased by ± 13.6%, and in patients with cirrhosis by ± 23.7% (Figure 3.2.1 and 3.2.2 Ultrasound of patients S.B., 55 years old, and T.K., 40 years old, with noticeable changes in the liver architecture and the diagnosis of cirrhosis) . The size of the spleen in patients with chronic hepatitis increased by ± 11.2%, and in patients with cirrhosis ± 18.4%. The portal vein in patients with chronic hepatitis increased by ± 8.6%, and in patients with cirrhosis by ± 21.3 % (Figure 3.2.1). Hepatosplenomegaly was observed in 43 patients, which contributed to the proposal of direct or indirect impact of COVID - 19 on patients suffering from chronic diffuse liver diseases. Newly diagnosed portal hypertension and the formation of free fluid in the abdominal cavity, ascites were detected in 23 patients, while these patients did not suffer from these complications before infection.

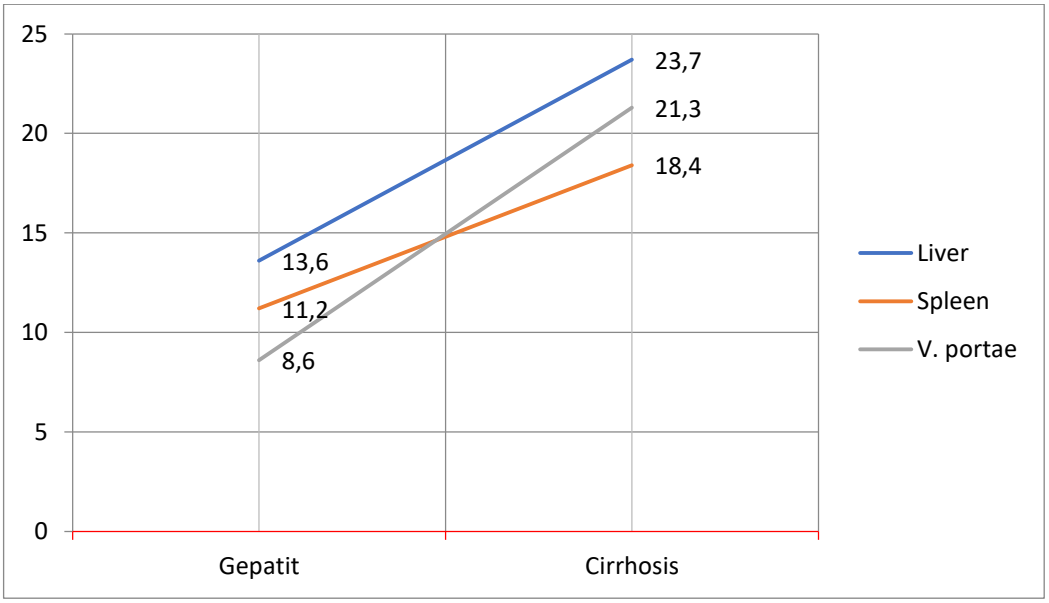


Diagram 3.2.1. ***Ultrasound shifts in indicators after COVID -19.***

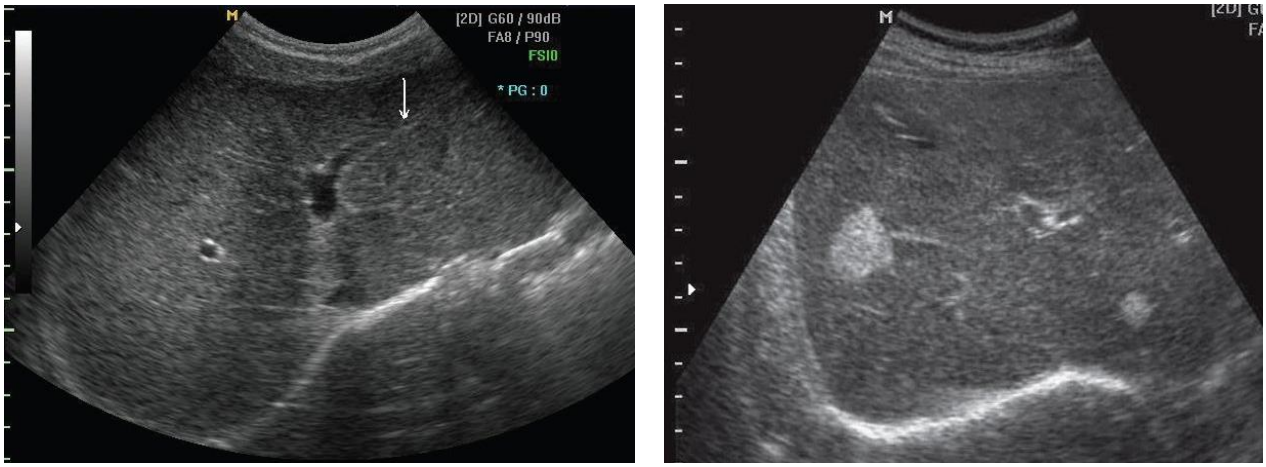


Fig. 3.2.1. Ultrasound of patient S.B. Diffuse changes in the liver parenchyma. CP. (heterogeneous echostructure). Hepatosplenomegaly. Portal hypertension. Free fluid in the abdominal cavity about 1000-1500 ml. Ascites.

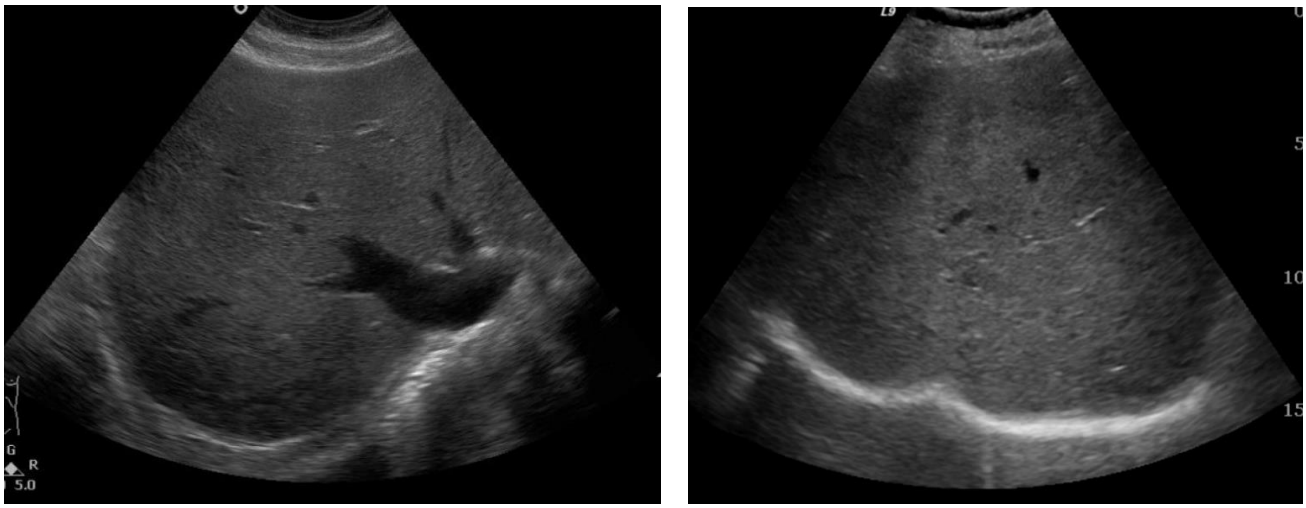


Fig. 3.2.2.Ultrasound of patient T.K. echo picture of liver cirrhosis. Portal hypertension. Splenomegaly. Significant amount of ascites.

Elastometry. FibroScan is a high-tech, non-invasive method for assessing liver fibrosis and steatosis based on shear wave elastography, which measures liver tissue stiffness in kilopascals (kPa) and the level of fatty liver infiltration, the so-called controlled attenuation parameter (CAP), expressed in decibels per meter (dB/m). The method is widely used in clinical practice for the diagnosis and monitoring of chronic liver diseases, including viral hepatitis B and C, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, autoimmune and

cholestatic hepatitis, as well as in patients with metabolic syndrome and diabetes mellitus. The basic principle of FibroScan is the generation of weak mechanical vibrations that cause shear waves, the propagation speed of which is recorded by an ultrasound sensor and depends on the tissue density: the higher the degree of fibrosis, the higher the stiffness and speed of the wave. Unlike liver biopsy, fibroscan allows examining a much larger volume of tissue, does not require hospitalization, is safe, painless and gives results immediately after the procedure, which makes it convenient for serial examinations and long-term monitoring. The results are interpreted using the METAVIR scale, where liver stiffness values of less than 5.5 kPa correspond to the norm, and values above 12.5 kPa indicate the presence of cirrhosis. At the same time, CAP is used to assess steatosis, where values above 290 dB/m indicate a severe degree of fatty infiltration. Despite its high clinical value, the method has limitations: decreased accuracy in patients with severe obesity (which is partially resolved by using a special XL probe), ascites, acute inflammatory liver diseases and in the presence of anatomical features. Nevertheless, fibroscan has proven itself to be the most important tool in modern hepatology, allowing timely detection of fibrosis at early stages, assessment of the risks of progression to cirrhosis and hepatocellular carcinoma, and decision-making on the initiation, continuation or correction of therapy. Its use significantly improves the quality of patient management, reduces the need for invasive interventions and improves the prognosis for chronic liver diseases.

The liver elastomerism test was performed on 60 patients . It was noted that before COVID -19 infection, the level of fibrosis in people suffering from chronic diffuse liver diseases was in a significantly satisfactory state (Fig 3.2.1). For example In 9 patients, the fibrosis level on fibroscan was F1 (7.11 kPa), in 23 patients, the fibrosis level on fibroscan was F2 (10, 13 kPa) , in 22 patients the fibrosis level on fibroscan was F3 (12 , 64 kPa), and stage 4 fibrosis (17.76 kPa) was detected in 6 patients .

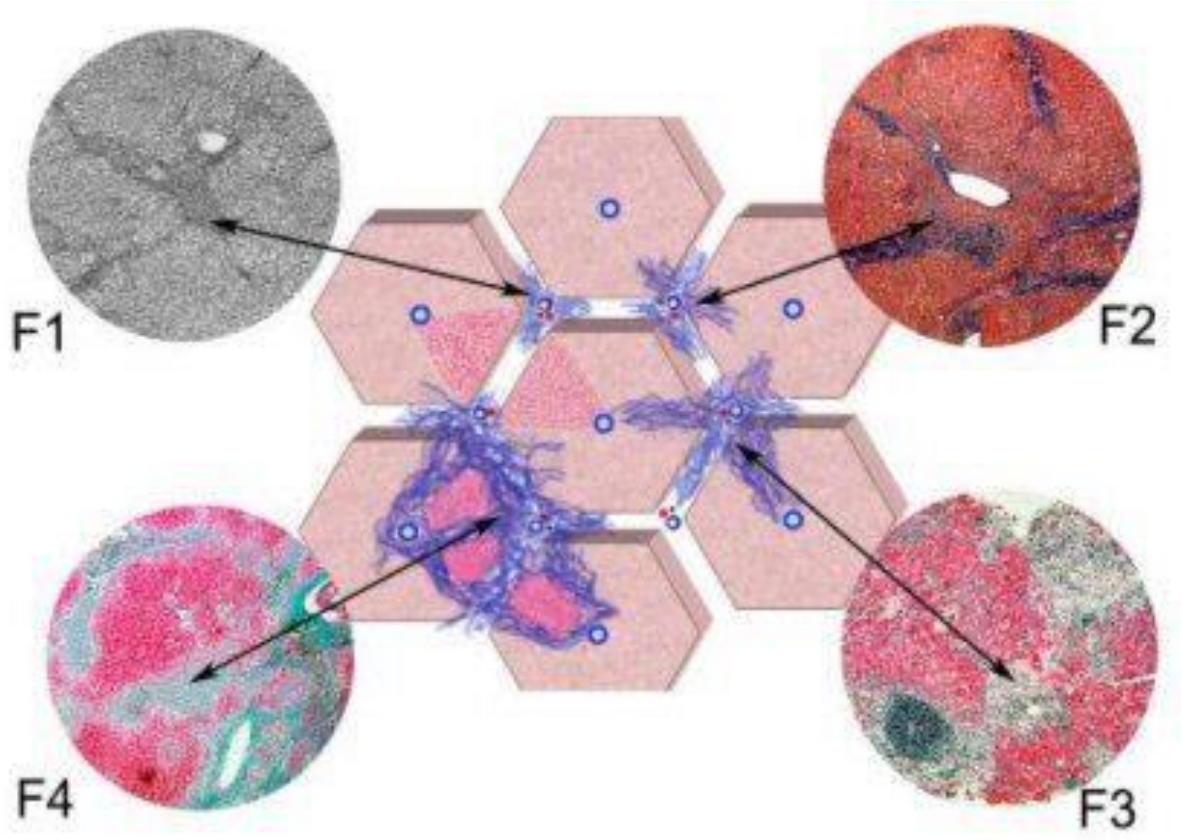


Fig. 3.2.1. Histological section of liver fibrosis

After infection, 6 patients were found to have elevated levels of F4 fibrosis (18 , 9 kPa), in 22 patients a transition from F3 to F4 was detected (16.81 kPa) , in 23 patients elastometry showed the presence of a transition from F2 to F3 (11.56 kPa) , in 9 patients a transition from F1 to F2 (10.68 kPa). Thus, in 6 patients the degree of fibrosis was F 1, in 14 patients F 2 was detected, F 3 was provided by 26, and with F 4 it reached the mark of 14 patients. A noticeable increase in fibrosis and changes in the architecture of the liver were observed after infection with COVID - 19 (diagram 3.2.2).

Noticeable changes were found in liver structures after COVID-19 infection. As can be seen from the elastometry readings, it is noticeable that COVID-19 can directly affect the liver structure (Figure 3.2.3, patient S.G., 71 years old) . Of the instrumental research methods, preference was given to elastometry, since it reveals the degree of fibrosis much better.

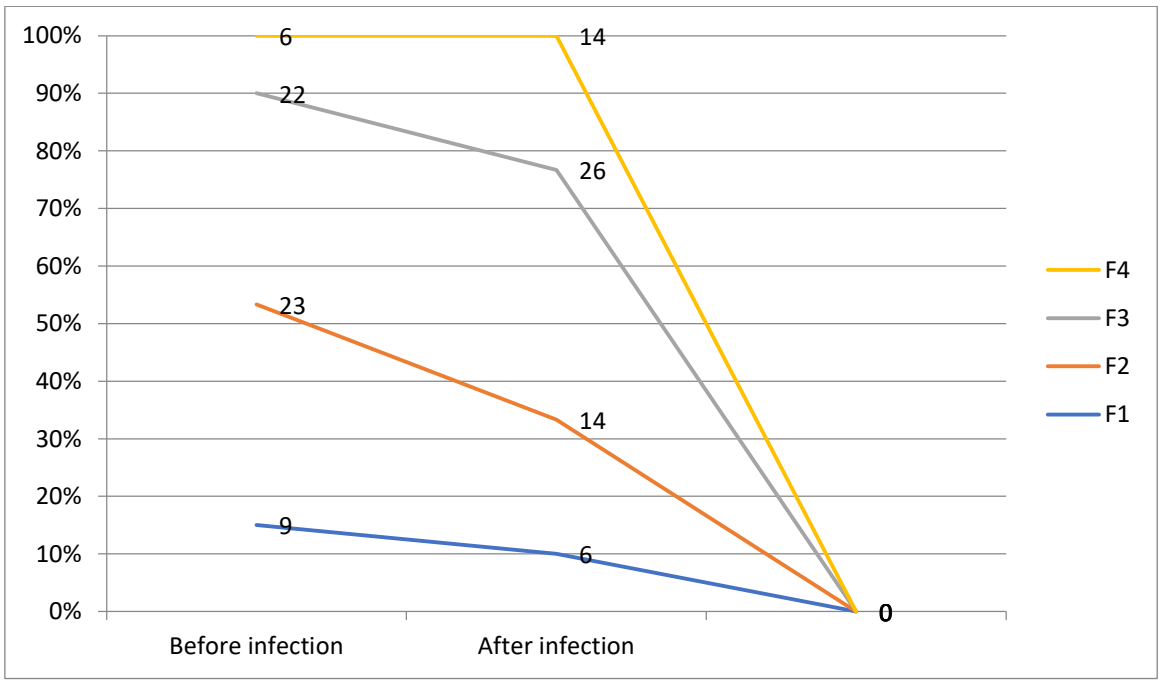


Diagram 3.2.2 ***Identification of elastometry indicators before/after the transferred COVID 19.***

Based on the data provided, it can be concluded that COVID-19 infection is accompanied by significant changes in the liver, especially in terms of fibrosis level. Different degrees of fibrosis were found, from F1 to F4, with the most severe changes observed in patients with F4 level. The level of fibrosis increases with the increase in its severity (from F1 to F4).

The most significant changes occur when moving from milder degrees of fibrosis (F1 and F2) to more severe ones (F3 and F4). For example, the transition from F3 to F4 is accompanied by a significant increase in the level of fibrosis from 16.81 kPa to 18.9 kPa.

Overall, a progressive pattern of changes is observed, suggesting that COVID-19 infection may worsen liver disease and lead to more severe degrees of fibrosis. Importantly, these changes in liver architecture may have serious clinical implications and require further monitoring and treatment to prevent progression of liver disease in COVID-19 patients.

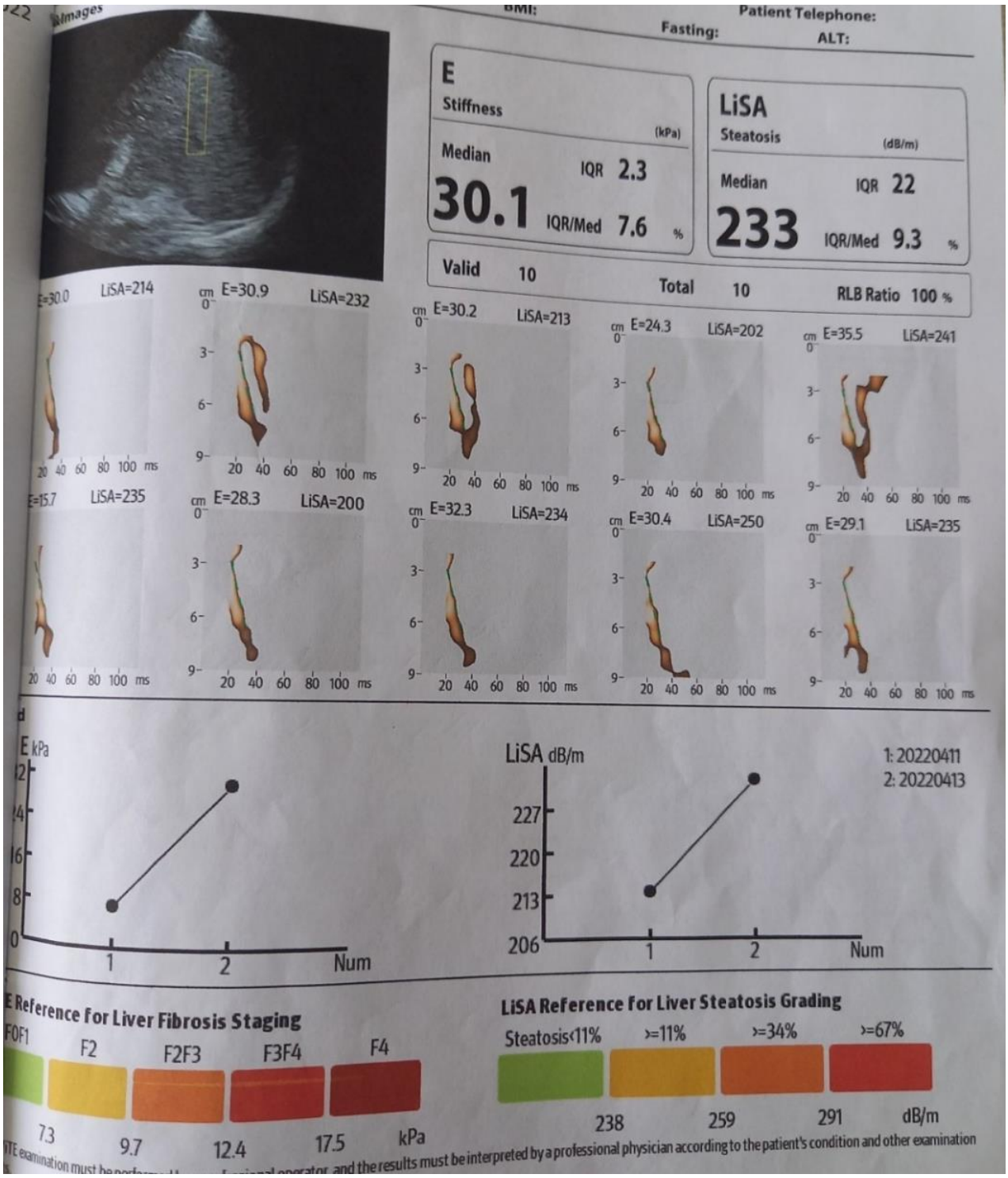


Figure 3.2.3 Patient S.G. CP. Fibrosis degree F 4.

Esophagogastroduodenoscopy. EGDS was performed in 32 patients, most of whom suffered from liver cirrhosis and transition to cirrhosis. Noticeable changes were observed in these subjects. In 17 patients, the following were detected: erosive gastritis, portal hypertension, esophageal varices (EV) (4 trunks) with transition to the cardia of the stomach,

complication of intermittent bleeding. In 8 patients, erosive bulbitis, chronic erosive antral gastritis were visualized. The remaining 7 patients were presented to the group: portal gastropathy, EV (3 degrees of severity), complication of intermittent bleeding.

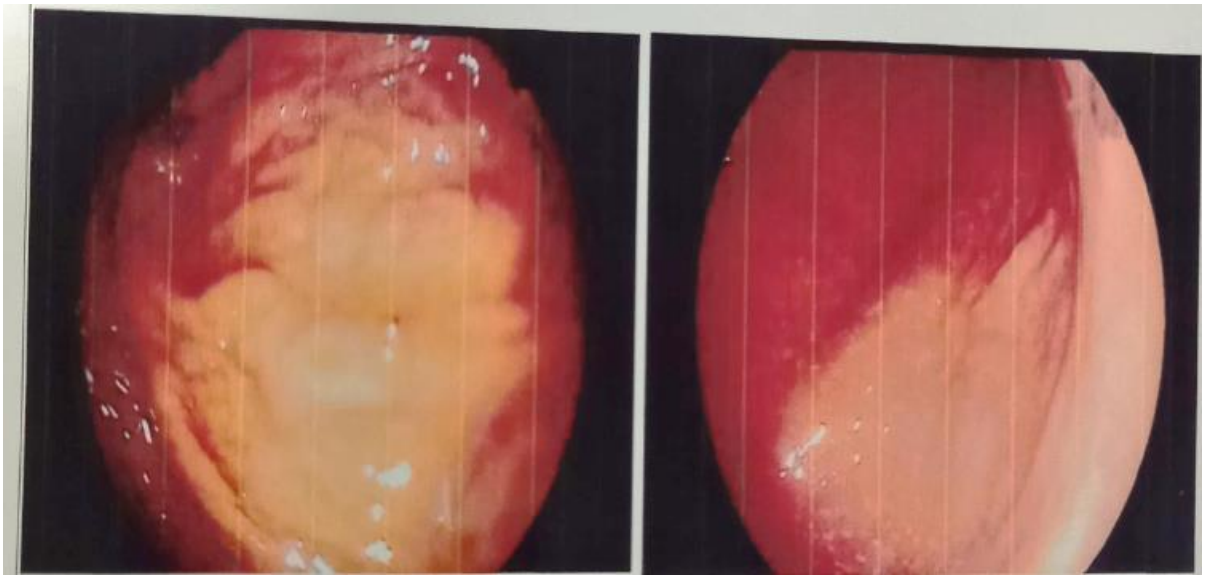


Fig. 3.2.1. Patient N.I. Erosive bulbitis, chronic erosive antral gastritis, esophageal varices (EV).

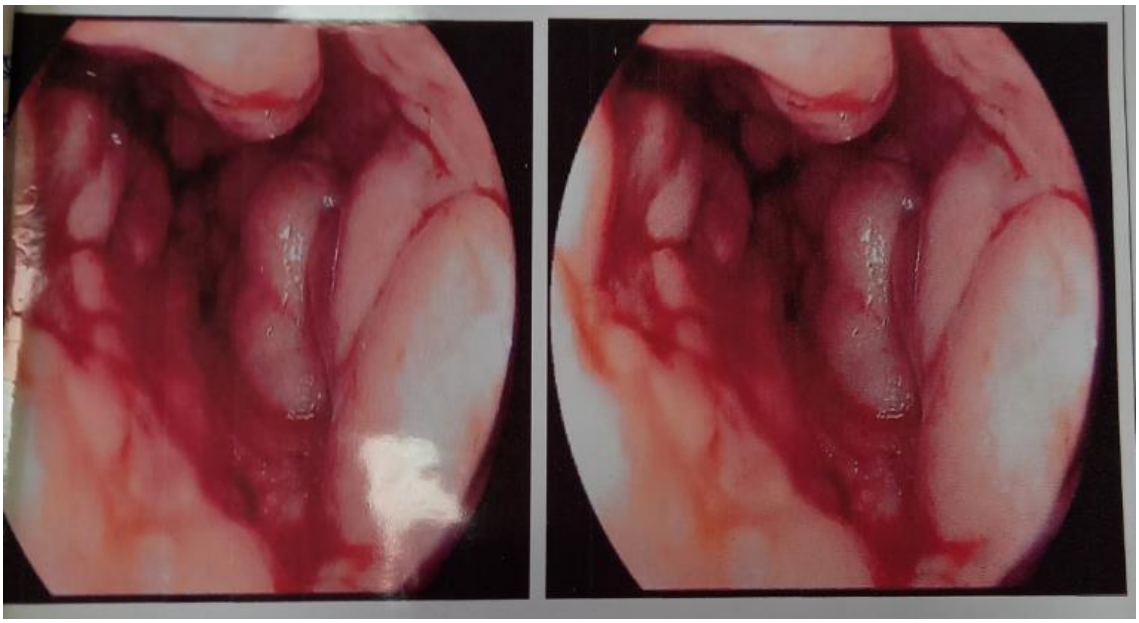


Fig. 3.2.2. Patient M.O. Erosive gastritis, portal hypertension, esophageal varices (EV) with transition to the cardia.

3.3. Clinical results of conservative treatment of patients with chronic kidney disease after COVID -19.

As noted above, the treatment was carried out by dividing the patients into 2 groups. In one group of people, 30 patients were treated according to the protocol, and the remaining 30 (15 patients with hepatitis and cirrhosis of the liver) were assigned and changed the assignment sheets with our approach. Significant differences appeared between the two groups both in the reduction of hospital days from 14 days to 8-10 days, and the condition of the patients themselves.

Table 3.3.1. Clinical changes after intensive therapy

Complications	Standard treatment (symptom reduction in % content)		Treatment suggested by the authors (symptom reduction in % content)	
	M	W	M	W
Ascites	16.3 %	12.1 %	28.7 %	31.5 %
Encephalopathy	15.4 %	18.1 %	36.1 %	29.6 %
Portal hypertension	19.2 %	17.8 %	30.6 %	33.3 %
Bleeding from varices	10.4 %	13.2 %	23.9 %	22.6 %
Coagulopathies	15.4 %	17.2 %	34.2 %	41.0 %

Based on the above table, it is concluded that the treatment tactics proposed by the authors have a positive effect on the condition of patients. The authors of the proposed therapy report significant positive dynamics in the treatment results. The use of this therapy was accompanied by a noticeable improvement in clinical parameters and a decrease in symptoms in patients. Positive changes were noted in the characteristics of the disease, including a decrease in viral load (if applicable), improved liver function, reduction or prevention of complications, and improved quality of life. These results

emphasize the effectiveness of the proposed therapy and confirm its potential for successful treatment of the disease. Patients who underwent the proposed therapy also noted a significant improvement in their general condition and a decrease in the intensity of disease symptoms. Clinical trials and monitoring of health parameters confirmed stable and gradual progress during treatment.

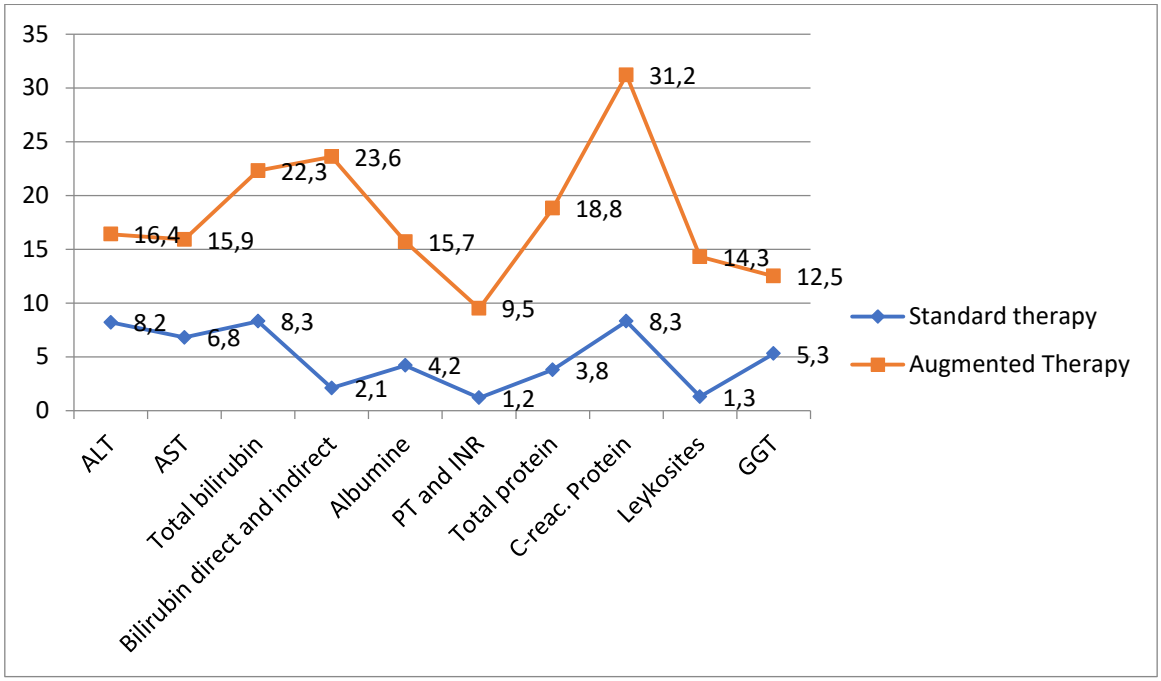


Diagram 3.3.1. **Comparative analysis of standard and proposed therapy in percentage reduction of laboratory parameters.**

Moreover, the proposed therapy has demonstrated its safety and good tolerability, minimizing possible side effects. An important aspect is not only the improvement of biomedical indicators, but also the increase in the level of patient satisfaction, which emphasizes the comprehensive success of this treatment approach. In addition, the results of the proposed therapy are marked by an improvement in laboratory parameters, such as normalization of liver function biomarkers and a decrease in inflammatory markers. Control studies also confirmed the stability of the achieved positive changes over time. The success of the therapy is based on a comprehensive effect on the main pathogenetic mechanisms of the disease, which contributes to more effective control and management of the patient's condition. In light of these results, the

proposed therapy can be considered a promising and prospective method in the treatment of this disease.

Conclusion to III chapter

The study of laboratory parameters in patients with chronic diffuse liver diseases (CDLD) against the background of COVID-19 provided important research data that allow us to better understand the impact of the virus on the characteristics of the disease and the effectiveness of conservative treatment.

The results of laboratory changes in patients with CDZD before and after COVID-19 infection revealed significant variations in biochemical and hematological parameters. Transient changes in the levels of transaminases, bilirubin, albumin and other liver markers highlight the impact of the virus on liver function in this population. It is important to note that these changes are due not only to the characteristics of CDZD itself, but also to the impact of COVID-19.

Clinical outcomes of conservative treatment of patients with chronic pulmonary disease after COVID-19 reflect the challenges of managing these conditions. A comprehensive approach including drug therapy, lifestyle changes, and monitoring appears to be effective but requires individualization based on changes in laboratory parameters and clinical status.

The study highlights the importance of further research into the impact of COVID-19 on the liver and optimal treatment strategies in patients with CDLD. The development of more accurate diagnostic and therapeutic methods can significantly improve the prognosis and quality of life of this patient population. The findings also highlight the importance of further research into the development of innovative diagnostic and therapeutic methods specifically tailored to the unique clinical features of patients with CDLD who have recovered from COVID-19 to optimize and personalize treatment approaches.

CHAPTER IV. METHODS OF PREVENTION AND TREATMENT OF CHRONIC LIVER DISEASES AFTER COVID-19

4.1. Approaches to preventing exacerbation of chronic liver diseases after COVID-19

Prevention of exacerbation of chronic liver diseases (CLD) after COVID-19 infection is an important task of modern medicine. SARS-CoV-2 infection, affecting the body, creates conditions for the activation of latent chronic processes, including liver diseases. Particular attention is paid not only to the treatment of existing pathologies, but also to the prevention of their exacerbations.

One of the most important aspects of prevention is vaccination against SARS-CoV-2. Studies show that vaccination reduces the risk of severe COVID-19 and reduces the likelihood of decompensation of chronic liver diseases. According to the WHO, vaccination can reduce the incidence of severe complications in patients with chronic liver diseases by 30-50%. Patients with conditions such as cirrhosis, viral hepatitis, and non-alcoholic fatty liver disease (NAFLD) are at increased risk. Vaccination in this population reduces the incidence of hospitalization and improves overall outcomes. For example, a 2021 study conducted in the United States showed that vaccinated patients with NAFLD had a 40% reduced risk of hospitalization compared to unvaccinated patients.

Diet therapy plays a central role in preventive measures. For patients with NAFLD, it is important to follow a diet low in saturated fat, sugar, and salt, and to increase the consumption of plant foods rich in fiber, vitamins, and antioxidants. Including omega-3 fatty acids in the diet, found in fish and flaxseed oil, helps reduce inflammation and maintain liver function. According to a meta-analysis published in 2020, omega-3 fatty acid intake reduces the level of inflammatory markers in 70% of cases in patients with NAFLD. Weight control is especially important for patients with NAFLD, as even a moderate weight loss (5-10%) can significantly improve liver function, as confirmed by numerous clinical studies.

Physical activity is also an important element of prevention. Moderate aerobic exercise, such as walking, swimming, or yoga, is recommended to improve metabolic processes, help reduce liver fat levels, and strengthen the immune system. According to a study published in the journal Hepatology in 2019, regular exercise reduces blood transaminase levels by 25–30% in patients with NAFLD. Individualizing an exercise program based on the patient's comorbidities ensures safety and effectiveness.

Quitting unhealthy habits such as alcohol and smoking is of utmost importance to prevent the progression of chronic liver disease. Alcohol increases inflammation and promotes fibrosis, while smoking impairs microcirculation and metabolism in the liver. According to the European Association for the Study of the Liver (EASL), quitting alcohol reduces the risk of cirrhosis progression by 50%. Consultations with specialists, including addiction specialists and nutritionists, can help patients quit unhealthy habits. Support programs such as Alcoholics Anonymous groups have also been shown to be highly effective in the long term.

Another area of prevention is stress management. Psycho-emotional stress associated with the pandemic can negatively affect the liver through activation of the hypothalamic- pituitary-adrenal axis. The use of relaxation techniques such as meditation, breathing exercises and cognitive behavioral therapy can reduce stress levels and improve the overall condition of the patient. According to a 2022 meta-analysis , regular meditation reduces cortisol levels by 20%, which has a positive effect on liver function.

Particular attention should be paid to the prevention of drug-induced liver injury. Many patients who have had COVID-19 receive extensive pharmacotherapy, including antibiotics, steroids, and antiviral drugs, which can negatively affect the liver. According to a 2021 study, 15-20% of patients who have had COVID-19 showed signs of drug-induced liver injury. The use of hepatoprotectors, such as essential phospholipids and silymarin preparations,

helps minimize drug-induced injury. Clinical data show that the use of hepatoprotectors reduces the risk of developing acute liver injury by 30-40%.

In addition, an important aspect of prevention is regular monitoring of the liver condition. Patients are recommended to take tests for transaminase levels (ALT, AST), bilirubin and albumin at least once every three months. Liver ultrasound and elastography help to assess the degree of fibrosis and promptly detect disease progression. Including these methods in the standard monitoring plan helps to reduce the likelihood of complications such as cirrhosis or liver failure.

Thus, prevention of exacerbations of chronic liver disease after COVID-19 requires a comprehensive approach, including vaccination, diet therapy, physical activity, quitting bad habits, stress management and monitoring the liver condition. The implementation of these measures can significantly reduce the risk of complications and improve the quality of life of patients.

4.2 Treatment of concomitant conditions

Treatment of comorbidities plays a key role in preventing exacerbations of chronic liver diseases (CLD). These conditions, including obesity, diabetes mellitus, hypertension, dyslipidemia, and viral hepatitis, can worsen liver damage, increasing the risk of decompensation and fibrosis progression. Comprehensive treatment of such patients can significantly improve the prognosis.

One of the most significant factors is obesity, which is closely associated with the development of non-alcoholic fatty liver disease (NAFLD). Weight loss is a key element of therapy. Clinical studies show that even a loss of 5-10% of body weight can lead to significant improvements in histological parameters in patients with NAFLD, including a decrease in steatosis and inflammation. Treatment methods include diet therapy, physical activity, and drug approaches. Drugs from the group of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, such as dapagliflozin, not only promote weight loss, but also reduce the level of

fat accumulation in the liver. Glucagon-like peptide-1 (GLP-1) agonists, including liraglutide and semaglutide, have a similar effect and also reduce inflammation. In one of the large clinical trials in 2022, semaglutide resulted in a 40% reduction in fatty liver infiltration in 68% of patients.

Diabetes mellitus is another important factor influencing the progression of liver disease. In patients with diabetes, the risk of fibrosis increases 2-3 times, which requires effective glycemic control. Metformin remains the first-line drug, as it lowers glucose levels and has an additional antifibrotic effect. In cases where metformin is contraindicated , SGLT-2 inhibitors or thiazolidinediones such as pioglitazone are an alternative. Studies show that pioglitazone reduces liver inflammation and improves insulin sensitivity, which is especially useful for patients with NAFLD and diabetes.

Arterial hypertension requires careful monitoring, as elevated blood pressure increases the risk of microvascular liver damage. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are the drugs of choice. They not only lower blood pressure, but also reduce inflammation and oxidative stress in the liver. According to a large meta-analysis , the use of ACE inhibitors reduces the risk of cirrhosis progression by 25%.

Dyslipidemia, which is often observed in patients with NAFLD, requires correction of blood lipid levels. Statins, such as atorvastatin and rosuvastatin, have proven their effectiveness in improving the lipid profile and reducing the risk of cardiovascular complications. However, their use in patients with liver cirrhosis requires caution due to the possible risk of hepatotoxicity. According to research data, statins are safe in 95% of cases with strict monitoring of liver enzymes.

Patients with chronic viral hepatitis require enhanced monitoring after COVID-19, as the viral infection may trigger activation of viral replication. In such patients, regular measurement of viral load and transaminase levels is necessary. In case of exacerbation, antiviral therapy should be intensified,

including the use of drugs with a low hepatotoxicity profile. For example, the use of entecavir or tenofovir in patients with hepatitis B allows for effective control of viral replication and reduces the risk of liver damage.

For patients with liver cirrhosis, an important direction of treatment is the prevention of decompensation. The administration of albumin infusions helps maintain colloid osmotic pressure and prevent the development of ascites. Control of sodium balance and restriction of salt in the diet are also important measures. Non-selective beta-blockers, such as propranolol and nadolol, are widely used to prevent portal hypertension, reducing the risk of bleeding from esophageal varices. If necessary, endoscopic treatment is performed, including ligation of varices.

Particular attention is paid to preventing infectious complications, as patients with cirrhosis are at high risk of bacterial infections. Prophylactic use of antibiotics such as norfloxacin reduces the incidence of spontaneous bacterial peritonitis by 30%. In addition, regular vaccination against pneumococcal infection and influenza virus helps reduce the risk of complications.

Regular monitoring by specialists is important for all patients with CDZD. Laboratory tests, such as determination of ALT, AST, bilirubin and albumin levels, as well as instrumental methods, including ultrasound and FGDS, allow timely detection of disease progression and adjustment of therapy. The use of modern methods, such as transient elastography (FibroScan), allows assessing the degree of fibrosis and predicting the risk of complications.

Thus, the treatment of concomitant conditions in patients with CDZD requires a comprehensive and interdisciplinary approach. Modern methods of therapy and monitoring allow to minimize the risk of complications, improve the quality of life of patients and extend their life expectancy.

4.3. Clinical guidelines for rehabilitation of patients with chronic liver diseases after COVID-19

Rehabilitation of patients with chronic liver diseases (CLD) after COVID-19 occupies a central place in the structure of restorative treatment, given the multiple consequences of the viral infection on the hepatobiliary system. The SARS-CoV-2 virus, affecting the liver through a direct effect on cells or indirectly through systemic inflammation, hypoxia and cytokine storm, causes damage that requires a comprehensive approach to recovery. The main goal of rehabilitation is to restore liver function, prevent the progression of the underlying disease and improve the quality of life of patients.

4.3.1. Diet therapy as a basis for rehabilitation

One of the first stages of rehabilitation is dietary correction aimed at supporting the liver and reducing metabolic stress. The recovery diet should be rich in easily digestible proteins, antioxidants, vitamins B and C, and trace elements such as zinc and selenium. Studies show that zinc deficiency is observed in 30-50% of patients with chronic liver diseases, and its correction helps improve the synthetic function of the liver.

A typical diet may include lean meats and fish, vegetables, fruits, whole grains, nuts, and vegetable oils. Antioxidant-rich foods such as berries, citrus fruits, spinach, and broccoli help reduce oxidative stress. In patients with portal hypertension and ascites, it is important to limit salt and fluid intake. It is recommended to consume no more than 2 g of sodium per day to prevent fluid retention. Additionally, specialized nutritional mixtures such as Nutricomp, which contain increased doses of protein and low sodium content, can be used.

4.3.2. Physical rehabilitation

Physical activity plays a key role in the rehabilitation of patients with NAFLD. Moderate physical activity helps improve blood circulation, strengthen the immune system, and normalize metabolism. According to research published in the journal Hepatology in 2021, regular exercise reduces intrahepatic fat levels by 20–30% in 6 months in patients with NAFLD.

It is recommended to start with light exercises, such as breathing exercises, walks in the fresh air or yoga, gradually increasing the intensity of the load. Patients with decompensated cirrhosis require a special approach and regular monitoring of their condition. For example, studies show that low-intensity training is not only safe for such patients, but also helps improve their physical fitness and reduce blood ammonia levels.

4.3.3. Psychological support

The COVID-19 pandemic has become a significant stress factor for many patients, especially for those who have faced a severe course of the infection and its consequences. Psychological support is an important component of rehabilitation. Working with psychologists, group sessions or art therapy can help improve mood, reduce anxiety and depression.

According to the World Health Organization, 40–50% of patients with chronic liver disease show signs of depression and anxiety. These conditions worsen overall adherence to treatment and can slow down the recovery process. Cognitive behavioral therapy, meditation, and stress management techniques have been shown to be highly effective in reducing cortisol levels and improving overall psychoemotional well-being.

4.3.4. Medication support

Medicinal support includes the use of hepatoprotectors, antioxidants and anti-inflammatory drugs. Preparations based on silymarin, ademetionine and essential phospholipids help restore liver cells, reduce the level of fibrosis and improve the general condition of the patient. For example, clinical studies show that the use of silymarin for 6 months reduces the level of transaminases by 35-40% in patients with CDZD.

In cases of inflammatory processes or complications, individual selection of therapy is recommended taking into account the clinical picture. Anti-inflammatory drugs such as pentoxifylline demonstrate effectiveness in reducing the level of inflammatory cytokines in patients with severe fibrosis.

4.3.5. Monitoring the condition of patients

Regular laboratory tests are an integral part of rehabilitation. Tests for ALT, AST, bilirubin, albumin and coagulogram levels allow us to assess the dynamics of liver recovery. According to a large meta-analysis of 2022, regular monitoring of these indicators reduces the risk of complications by 25% due to timely correction of therapy.

Instrumental diagnostic methods such as liver ultrasound, elastography (FibroScan) and upper gastrointestinal endoscopy allow to detect structural changes in the liver and complications such as esophageal varices. In patients with cirrhosis, FibroScan is recommended every 6 months to monitor fibrosis progression.

4.3.6. Educational programs for patients

One important element of rehabilitation is teaching patients the basics of a healthy lifestyle and self-monitoring. Conducting educational programs that include information on proper nutrition, physical activity, and the need for regular monitoring helps to increase adherence to treatment. For example, in a 2020 study in Germany, educational programs for patients with liver cirrhosis improved adherence rates by 45%.

Rehabilitation of patients with chronic liver diseases after COVID-19 should be comprehensive and individualized. The use of diet therapy, physical activity, psychological and drug support, as well as regular monitoring can significantly improve treatment outcomes. The inclusion of educational programs increases patient awareness and promotes long-term remission.

4.4. Innovative methods and prospects for the treatment of chronic liver diseases after COVID-19

Modern research is actively aimed at developing innovative methods for treating chronic liver diseases (CLDs) that have been exacerbated or caused by COVID-19 infection. The main emphasis is on the use of regenerative medicine technologies, molecular biology, nanotechnology and personalized therapy.

These areas make it possible to create new approaches to treatment that can minimize the consequences of liver damage and improve the quality of life of patients.

4.4.1. Regenerative medicine: stem cells

One of the most promising methods is the use of mesenchymal stem cells (MSCs) to restore damaged liver tissue. MSCs have a high differentiation capacity, anti-inflammatory effect, and stimulate tissue regeneration. Studies show that the introduction of stem cells to patients with liver cirrhosis improves organ function in 60-70% of cases. For example, a study conducted in China in 2020 showed that the use of MSCs in patients with decompensated liver cirrhosis reduces bilirubin levels by 30% and improves liver synthetic function.

In addition to MSCs , induced pluripotent stem cells (iPSCs) are being actively studied. These cells can be reprogrammed from the patient's somatic cells and used to replace damaged hepatocytes. This method is promising for patients with genetically determined liver diseases.

4.4.2 Cytokine inhibitors and inflammation modulation

Cytokine inhibitors, such as drugs that block interleukin-6 (IL-6) or tumor necrosis factor-a (TNF-a), are becoming increasingly popular in the treatment of severe liver disease associated with inflammation. These drugs effectively reduce the activity of the cytokine storm, which is the main mechanism of liver injury in patients with severe COVID-19.

For example, the use of tocilizumab, an IL-6 inhibitor, in patients with COVID-19 and concomitant CDD demonstrated a 50% reduction in inflammatory markers (CRP, ferritin) after just 10 days of therapy. Drugs from this group have also shown their effectiveness in preventing fibrosis progression.

4.4.3. Gene therapy and genome editing technologies

Genome editing technologies such as CRISPR-Cas9 are opening up new horizons in the treatment of LDLD. They can eliminate genetic mutations that underlie certain liver diseases, such as Wilson's disease or hereditary hemochromatosis. For example, in 2021, clinical trials of CRISPR therapy for patients with antitrypsin deficiency resulted in significant improvements in liver function.

Gene therapy also involves the use of adeno-associated viruses (AAV) to deliver genetic material that can restore liver function. Studies show that this method is safe and effective in treating rare genetic liver diseases, but its use requires further clinical trials.

4.4.4. Nanotechnology in hepatology

The use of nanotechnology opens up new possibilities in the delivery of drugs directly to liver cells. Nanocapsules and nanoparticles containing active substances help to minimize systemic side effects and increase the effectiveness of therapy. For example, the development of nanoparticles with ursodeoxycholic acid allows for a 1.5-fold increase in its bioavailability and an improvement in the antifibrotic effect.

In addition, gold and silver-based nanoparticles are being explored as platforms for delivering antioxidants and anti-inflammatory drugs. These technologies are in preclinical trials but have already shown promising results in animal experiments.

4.4.5. Personalized medicine and biomarkers

A personalized approach to treatment is becoming the basis of modern hepatology. The use of biomarkers allows us to predict the course of the disease and select the most effective methods of therapy. For example, measuring the level of microRNA (miRNA-122) in the patient's blood makes it possible to assess the degree of liver damage and the effectiveness of the therapy.

Biomarkers are also used to predict treatment response. For example, in patients with NAFLD, genetic polymorphism of the PNPLA3 gene helps

determine the risk of disease progression and select the most appropriate therapeutic regimen.

4.4.6. Innovative hepatoprotectors

Modern hepatoprotectors are developed using the latest achievements in pharmacology. Preparations based on mitochondrial antioxidants, such as "Mitochondrion", show high efficiency in protecting liver cells from oxidative stress. Clinical studies demonstrate a 40% reduction in transaminase levels after three months of treatment.

Another direction is the development of drugs that promote the restoration of hepatocytes. For example, the use of molecules that activate liver growth factors (HGF) stimulates tissue regeneration and reduces fibrosis. These drugs are at the clinical trial stage, but are already showing encouraging results.

Innovative treatments for chronic liver diseases after COVID-19 offer new opportunities to improve the effectiveness of therapy, prognosis, and quality of life for patients. However, their widespread implementation requires further research, development of treatment standards, and availability of new technologies. Thanks to modern advances in regenerative medicine, genetics, and nanotechnology, the future of CLD treatment looks promising.

Conclusion to Chapter IV

Chapter IV presents a comprehensive analysis of methods for the prevention, treatment, and rehabilitation of patients with chronic liver diseases (CLD) after COVID-19 infection. The presented data emphasize the importance of an integrated approach that combines vaccination, diet therapy, physical activity, correction of concomitant diseases, and innovative treatment methods. The relevance of the chapter is due to the serious consequences of COVID-19 for patients with CLD, including an increased risk of decompensation, fibrosis progression, and complications.

Prevention of exacerbations of chronic liver diseases is central to the post-COVID strategy. Vaccination, as the main tool for preventing severe infection, has proven effective in reducing the incidence of complications in patients with chronic liver disease, including cirrhosis, viral hepatitis, and non-alcoholic fatty liver disease. An important component of prevention is adherence to healthy eating principles aimed at reducing inflammation, controlling body weight, and improving metabolic processes. Additionally, regular physical activity and giving up bad habits help strengthen the immune system, improve liver function, and prevent further damage.

Treatment of comorbid conditions such as obesity, diabetes mellitus, hypertension and dyslipidemia plays an important role in the management of CDLD. The use of modern pharmacological agents such as SGLT-2 inhibitors, GLP-1 agonists and ACE inhibitors demonstrates high efficiency in reducing inflammation, improving metabolic processes and preventing fibrosis progression. These approaches require individualization of therapy and regular monitoring, which ensures safety and improved outcomes.

Rehabilitation of patients with chronic liver diseases after COVID-19 includes diet therapy, physical activity, psychological support, drug treatment and regular monitoring of the liver condition. Restoration of liver function requires a systematic approach based on the use of nutritional support, specialized exercises and modern hepatoprotectors. Additional attention is paid to managing stress and depressive states, which can slow down the recovery process. Inclusion of educational programs for patients promotes their adherence to treatment and increases awareness of the need for regular health monitoring.

Innovative treatments such as regenerative medicine, gene therapy, nanotechnology and personalized approaches open up new possibilities for effective management of chronic liver diseases. The use of mesenchymal stem cells, cytokine inhibitors, genome editing and drug-containing nanocapsules not only minimizes the effects of liver damage but also promotes its restoration.

These technologies, being at the forefront of medical science, represent a promising prospect for patients with severe liver diseases.

Thus, methods of prevention, treatment and rehabilitation of chronic liver diseases after COVID-19 require a systemic and interdisciplinary approach. The data presented in the chapter emphasize the importance of early intervention, the use of modern technologies and continuous monitoring of patients. This approach allows not only to minimize the risks of complications, but also to significantly improve the quality of life of patients, ensuring long-term positive results.

CONCLUSION

There are many possible harmful effects of coronavirus infection on the liver. It is no secret that SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE-2) in the guise of a receptor to penetrate the intracellular environment. It was found that ACE-2 is expressed to a greater extent on cholangiocytes, which makes the liver a possible target for the virus. Liver biopsy in patients with atypical pneumonia with SARS-CoV 2002 indicated a numerous increase in mitotic cells with eosinophilic bodies and balloon-like hepatocytes, which suggested the idea that SARS-CoV can induce hepatocyte apoptosis and provoke liver damage. Many studies have shown that SARS-CoV, through its specific protein 7a, can induce apoptosis at subcellular levels in various organs (including lung, kidney, and liver) in a caspase-dependent manner, suggesting that SARS-CoV may directly target liver tissue.

The work is based on the analysis of studies conducted on 60 patients who underwent inpatient treatment in the general intensive care unit of the Republican Scientific Center for Emergency Medical Care and in the hepatology department of the infectious diseases regional hospital of the Bukhara region for the period from 2021 to 2024.

A total of 60 patients were divided into two groups: 30 (50%) with liver cirrhosis and 30 (50%) with hepatitis, including 28 (47%) men and 32 (53%) women who had recovered from COVID -19. There were 10 male and 20 female patients with hepatitis. There were 16 male and 14 female patients with liver cirrhosis. The distribution by gender did not reveal any significant difference between men and women in the total number, however, most women had bleeding from esophageal varices (6) and peptic ulcer (11), while 6 men had elements of encephalopathy.

An analysis of clinical indicators was conducted to identify the features of the clinical course of LC and hepatitis against the background of COVID -19 in patients with diffuse liver diseases in comparison with the data of a similar examination of patients without signs of liver pathology. For this purpose, we

studied the results of clinical, biochemical and instrumental research methods of 60 patients aged 14 to 73 years.

We have studied in detail the impact of the SARS-CoV-2 virus on the course of chronic diffuse liver diseases. The results allow us to identify the features of clinical manifestations and changes in the liver in patients who have had COVID-19, which is important in the context of assessing the prognosis and developing effective treatment strategies.

We analyzed the role of drug-induced hepatotoxicity and drug-drug interactions in the context of chronic diffuse liver diseases in the context of COVID-19. The identified interactions and potential risks of hepatotoxicity will serve as the basis for recommendations on the safe use of drugs in this group of patients.

Our research allowed us to develop prognostic criteria for chronic diffuse liver diseases in the context of COVID-19. We also identified effective treatment methods that take into account the specific effects of the virus on the liver and combinations with other drugs.

Taken together, our results not only expand our understanding of the impact of COVID-19 on chronic liver disease, but also provide a basis for determining prognosis and developing optimal treatment strategies. The findings may be used to improve clinical practice and support decision-making in the care of patients with chronic diffuse liver disease after COVID-19.

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