
# Chronic Liver Diseases And Humoral Factors Of Immunity

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ABSTRACT

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

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

Epidemiological evidence suggests that patients with metabolic disorders and chronic diseases are most susceptible to SARS-CoV-2 [4,5,10]. It has been suggested that non-structural proteins of SARS-CoV are capable of modifying the structure of hemoglobin in the erythrocyte, which leads to disruption of oxygen transport, causes iron dissociation, porphyrin formation, and an increase in ferritin. Such exposure can lead to increased inflammation in the lungs, oxidative stress, hypoxemia, hypoxia, the development of symptoms of acute respiratory distress syndrome (ARDS) and multiple organ oxygen deficiency [5]. People with serious chronic medical conditions, including patients with liver disease, are at higher risk of severe illness from the virus [4]. 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. In response to the spread of coronavirus, the development of a hyperimmune reaction is observed - the so-called "cytokine storm", characterized by the synthesis of a significant (abnormal) amount of pro-inflammatory interleukins (IL-1β, IL-6, tumor necrosis factor, etc.) and chemokines with a simultaneous decrease in the content of T- lymphocytes in the blood [1,2,3]. In addition, SARS-CoV-2, infecting the endothelium of blood vessels, interacts with ACE2 located there and leads to the development of endothelial dysfunction, hyperpermeability, microcirculation disorders, the development of vascular thrombophilia and thrombus formation [6,7,8,11].

Changes in liver function parameters found in COVID-19 are associated with the progression and severity of the infectious process. The mechanism of direct cytotoxicity due to active replication of SARS-CoV-2 in hepatocytes is not entirely clear and, apparently, is due to possible proliferation of hepatocytes, liver damage in response to systemic inflammation, and the development of drug-induced hepatotoxicity [10,12,15]. In earlier studies related to infection

with coronaviruses of the Betacoronavirus genus (SARS-CoV (2002–2003) and MERS-CoV (2012)), liver damage was quite common and associated with disease severity [9,16]. As is known, SARS-CoV, as well as SARS-CoV-2, use ACE2 as receptors for entry into cells, which are widely distributed in the cells of the heart, kidneys, blood vessels, especially alveolar epithelial cells, as well as the liver, pancreas, intestinal epithelium, which ensures systemic damage [17,19]. However, it is not entirely clear whether liver damage can be caused directly by the SARS-CoV-2 coronavirus. Previous RNA-seq sequencing data in the Human Protein Atlas Database support the expression of ACE2 in SARS-CoV liver [9]. Moreover, a low frequency of ACE2 expression is observed only in cholangiocytes, but not in hepatocytes, Kupffer cells or endothelial cells. In addition, SARS-CoV, through the specific protein 7a, is capable of inducing apoptosis in cell lines of various organs (including lungs, kidneys, liver) in a caspase-dependent manner. This indicates the possibility of direct effects of SARS-CoV on liver tissue. The expression of ACE2 in liver tissue in relation to the novel coronavirus was analyzed based on RNA sequencing data. Objective assessment of ACE2-specific expression in healthy liver tissue based on RNA-seq data from two independent cohorts identified ACE2-specific expression on cholangiocytes and minimally in hepatocytes.

The results showed that the virus is able to directly bind via ACE2 to cholangiocytes, but not necessarily to hepatocytes [11,18]. The level of ACE2 expression in bile duct cells is significantly higher than in hepatocytes, but comparable to the level in type 2 alveolar cells in the lungs, making the liver a potential target for the virus [12]. Based on these data, it can be assumed that abnormalities in liver biochemical parameters in patients with COVID-19 are not associated with damage to hepatocytes, but with dysfunction of cholangiocytes and other causes, such as drug hepatotoxicity and systemic inflammatory response, causing liver damage.

The purpose of the study was to study humoral factors in patients with liver cirrhosis and chronic hepatitis who had Covid 19.

**Materials and methods of research.** In the general therapy department of the multidisciplinary clinic of the Tashkent Medical Academy, 60 patients aged 30-65 years (average age 40.5 years) suffering from liver cirrhosis and chronic hepatitis were examined. Of these, 40 patients with liver cirrhosis were selected - the observation group (23 men and 17 women) and 20 patients (9 men and 11 women) with chronic hepatitis who had suffered Covid 19 - the main group. All patients were subjected to a full laboratory and instrumental examination: ultrasound examination of the abdominal organs, endoscopy, fibroscanning of the liver, ECG, MSCT (as indicated); laboratory tests included a general blood test, a general urinalysis, a biochemical blood test: ALT, AST, bilirubin, total protein, albumin, urea, creatinine, lipid profile, blood electrolytes (potassium, calcium, sodium), iron, blood sugar. Immunological studies were carried out by studying the levels of IgG, IgA, IgM, IFN α, IFN γ in blood serum using ELISA according to the attached instructions. The test systems of Vector Best LLC, (RF) were used. The research materials were subjected to statistical processing using Student's t-test using the standard Windows 2000 statistical software package.

**Research results and discussion.** In the observation group, men accounted for 56%, women - 46%, in the main group - 11% men and 59% women. Body mass index (BMI) in men of the main group (29.4±0.5 kg/m2) exceeded this indicator in women (26.1±0.4 kg/m2, p=0.023), while women were significantly older men (42.6±1.3 vs. 37.4±0.8, p=0.04). In the observation group, BMI in men was 32.3±0.6 kg/m2, which is higher than in women 28.4±0.5 kg/m2, p=0.02), and no significant difference was found by age - women on average at age 44.7±1.1 versus 46.4±1.2. Among the concomitant pathologies in patients, the following were noted: hypertension in 21% of cases in the observation group. There were no significant differences in the results of a general blood test, with the exception of the level of leukocytes, which was higher in men (p = 0.05) of both groups than in women and remained

within the normal range. The level of gamma-glutamyl transpeptidase (GGTP) in patients of the main group (85.2±4.8 U/l) was almost 2 times higher than this indicator in patients of the observation group (48.3±4.4 U/l, p=0.001) . Higher values of ALT (p=0.001), serum iron (p=0.049) and cholesterol (p=0.001) were found in patients with chronic hepatitis who had Covid 19. During the examination of patients with liver cirrhosis, it was found (observation group) that patients with minimal fibrosis F0–1 prevailed - 40.4% of cases, F2 fibrosis was detected in 27.2% of cases, F3 - in 17% of cases and F4 - in 15. 4%. In patients of the main group, a similar picture was observed: F0–1 - 52.1% of cases, F2 was detected in 25.1% of cases, F3 - in 8.8% of cases and F4 - in 14% of cases.

It is extremely difficult to diagnose stage I liver steatosis based on laboratory parameters in patients with chronic hepatitis, since significant differences were detected only in the level of triglycerides: with S0 - 1.4±0.09, and with S1 - 1.9±0.2 ( p<0.001). A direct moderate correlation was established between the degree of steatosis and the stage of fibrosis (p <0.001). The progression of liver fibrosis in patients with liver cirrhosis affected not only the activity of transaminases, but also lipid and carbohydrate metabolism. Thus, the level of blood triglycerides was minimal at the fibrosis stage F0–1 and amounted to 1.9±0.2 mmol/l, and at the fibrosis stage F2 – 2.1±0.1 (p<0.001). The maximum values were determined at the F3–F4 stage (2.8±0.1 mmol/l, p<0.001). In 85.6% of patients with liver cirrhosis, concomitant gastrointestinal diseases were identified, of which non-alcoholic fatty liver disease (NAFLD) was detected in 55.4% of cases according to the results of PLP, chronic cholecystitis in 42.3%, chronic pancreatitis in 18.5% of cases, ulcerative disease of the stomach and duodenum – 23% of cases. Patients with chronic hepatitis who have had Covid 19 are more likely to have obesity and hypertriglyceridemia in 62% of cases, hypertension in 56% of patients, chronic cholecystitis in 33% of patients. Liver pathology is accompanied not only by disturbances in lipid metabolism, but also in carbohydrate metabolism.

Type 2 diabetes mellitus was detected in 17% (n=7) of patients with liver cirrhosis and was significantly more often recorded at stages of liver fibrosis F3-F4 (p <0.01), and in patients who had Covid 19, type 2 diabetes mellitus was diagnosed in 65 % (n=13), but fibrosis was marked F2-F3. Of course, metabolic disorders in patients with chronic hepatitis significantly aggravate the course of the disease and require a more thorough and in-depth medical examination before prescribing treatment. Patients with such an unfavorable comorbid background require a personalized approach taking into account lifestyle, diet and fasting-dietary therapy, as well as more extensive laboratory monitoring.

In patients with chronic hepatitis aggravated by NAFLD, severe liver fibrosis (F3–F4) is significantly more often detected (up to 71% of cases) than in the group of patients without liver steatosis (p = 0.009). Our data are consistent with the results obtained by other researchers [11], who proved that the formation of hepatic steatosis is associated with genotype 3 of the virus and the relative risk of its occurrence is 2 times higher than in patients with chronic hepatitis with genotype 1 (RR 2.0; 95% CI 1.4–2.97), while high levels of C-reactive protein are recorded against the background of liver steatosis [9].

In patients with liver cirrhosis, aggravated by NAFLD, liver fibrosis of moderate intensity - F2 (54%) is significantly more often detected than in the group of patients without liver steatosis (p = 0.008), but in the presence of diabetes mellitus. In patients with diabetes mellitus, severe F 3-F4 fibrosis prevailed in 71.5% of cases.

Taking into account the identified correlations between the degree of steatosis and the stage of liver fibrosis, as well as the significant impact of Covid-19 on the course of the pathological process in the liver, a study of the influence of immunological parameters on the course of the disease was carried out (Table 3). As a result of a study of patients with chronic hepatitis, survivors of Covid 19 and suffering from liver cirrhosis, several new laboratory patterns were identified in the nature of immunological changes depending on the stage of liver fibrosis,

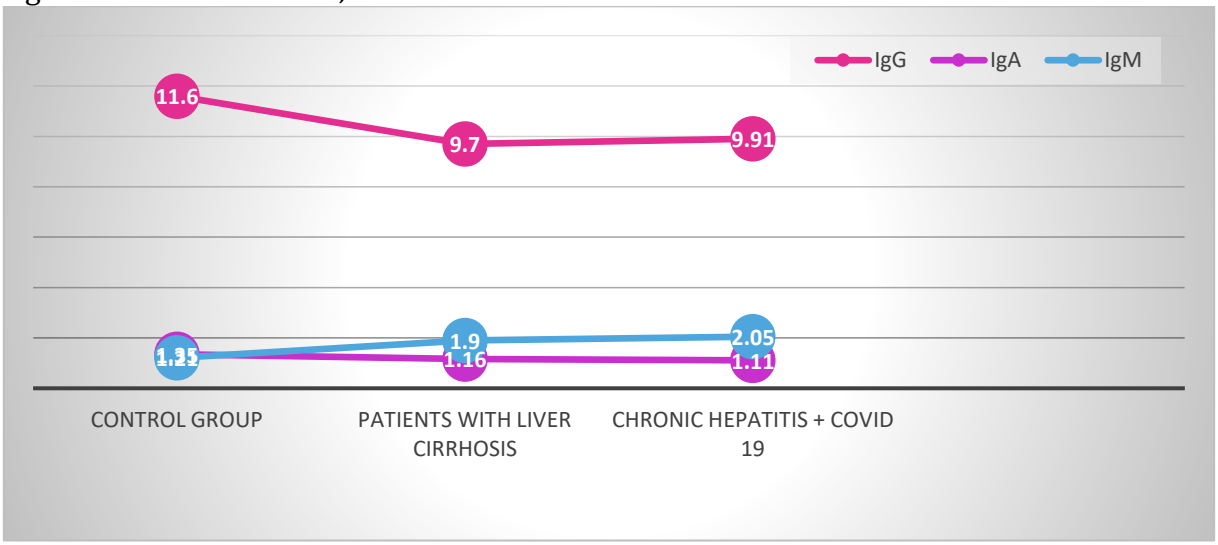
requiring comprehension and more detailed study.

Table 3.
Level of immunoglobulins, IFN α and IFNγ in the examined patients, (M±m)

| Indicators | Control group, n=30 | Liver cirrhosis, n=40 | CR hepatitis + Covid-19, n=20 |
|---|---|---|---|
| IgG, g/l | 11,6 ± 0,43 | 9,7 ± 0,33* | 9,91 ± 0,69*^ |
| IgA, g/l | 1,35 ± 0,2 | 1,16 ± 0,05* | 1,11 ± 0,06* |
| IgM, g/l | 1,21 ± 0,12 | 1,9 ± 0,26* | 2,05 ± 0,47*^ |
| IFN α, pg/ml | 31,7±2,6 | 37,16±2,18* | 39,2±1,58 |
| IFNγ, pg/ml | 25,2±1,8 | 36,16±3,05* | 34,5±1,82 |

Note: *Values are reliable in relation to the control group
^Values are reliable in relation to the group with cirrhosis
(p<0.05-0.001)

Analysis Of The Dependence Of Immunity Parameters On The Stage Of Liver Fibrosis Showed That In Patients With Liver Cirrhosis At The Stage Of Fibrosis F3–F4, There Was A Significant Decrease In Igg Compared With Its Level At Fibrosis F1–F2 (P = 0.031; P = 0.021). And In Total, In Patients With Liver Cirrhosis, The Level Of Igg Was 9.7 ± 0.33 G/L, Which Is Significantly Lower Than The Values In The Control Group (11.6 ± 0.43 G/L), P < 0.05. A Similar Picture Was Observed When Analyzing Iga Secretion - If In The Control Group The Numbers Were 1.35 ± 0.2 G/L, Then In The Observation Group - 1.16 ± 0.05 G/L, P < 0.05. A Decrease In The Secretion Of Ig A, Especially At The Stage Of Fibrosis F3–F4, Indicates CTL Insufficiency, Which Can Stimulate The Process Of Fibrosis And Indicates The Inactivity Of The Process At The Present Time. Multiple Comparisons Of Ig M Parameters In Patients With Liver Cirrhosis Showed An Increase In Secretion Along With The Severity Of Fibrosis (R = 0.451, P = 0.008); A Significant Excess Of This Indicator Was Found In Patients With F4 Fibrosis Compared To That In Patients With F0-1 (P = 0.024 , Mann-Whitney Test). And In Comparison With The Control Data - 1.21 ± 0.12 G/L, The Numbers Were As Follows - 1.9 ± 0.26 G/L, P <0.05. An Increase In Igm Secretion In Liver Cirrhosis Indicates A Viral Etiological Factor In The Development Of This Pathology.



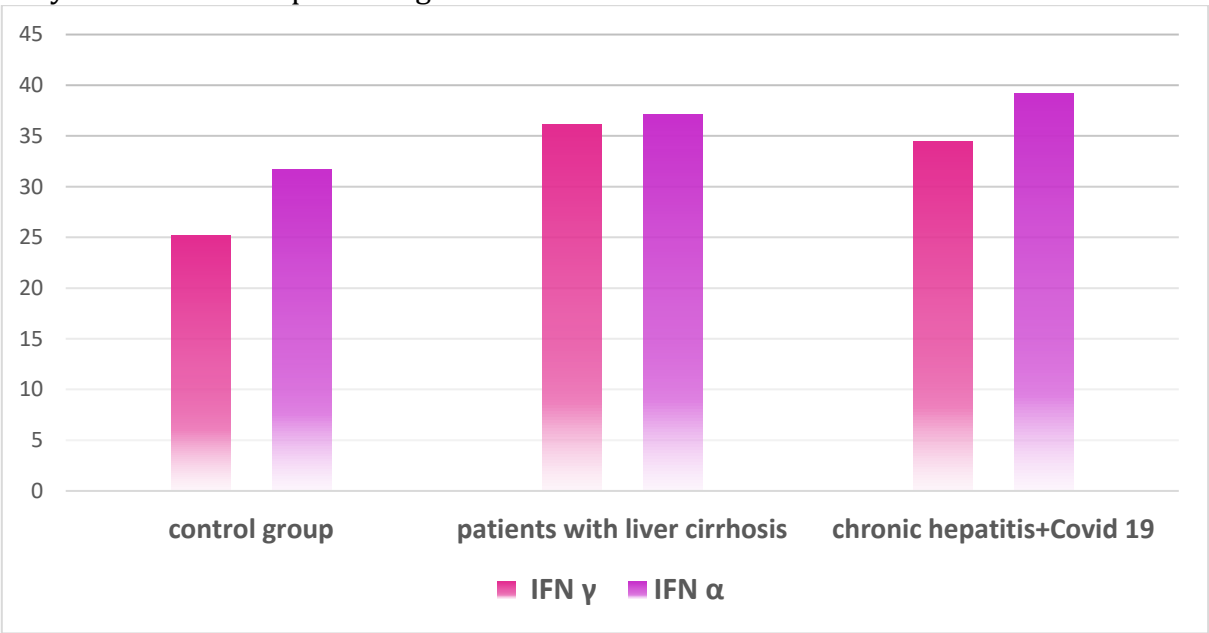

Rice. 1 Indicators of humoral immunity in patients with chronic hepatitis + Covid19 and liver cirrhosis.

Analysis of the immune status of patients with chronic hepatitis who have had Covid-19 with fibrosis stage F0–1 is characterized by a slight decrease in the total amount of Ig G and Ig A. At fibrosis stage F3-F4, a lower content of IgA was

noted, not only in comparison with control values, but also in comparison with a group of patients with liver cirrhosis, which gives grounds to conclude about the possible influence of Covid-19.

Studies of the cytokine spectrum may have important prognostic significance in chronic liver diseases. It was found that in patients with chronic hepatitis, survivors of Covid-19 and patients with liver cirrhosis, significant differences in the levels of circulating IFN-α and IFN-γ were detected. An increase in the concentration of IFN-γ was characteristic mainly for the later stages of chronic hepatitis disease (F3-F4), which was confirmed by statistically significant differences between groups F1 and F4 ($p < 0.05$), as well as F2 and F4 ($p < 0.05$). 05). There was a direct statistically significant relationship ($r=0.25$; $p=0.05$) between the degree of fibrosis and the level of IFN-γ. It is assumed that progressive liver damage by an additional provoking factor - covid intoxication - correlates with an increase in the level of intrahepatic Th type 1 cytokines (IFN-γ) [7,15].

There was a significant increase in the level of IFN-α in the compared groups compared to control data - 31.7 ± 2.6 pg/ml, in the group with liver cirrhosis - 37.16 ± 2.18 pg/ml, and in the group of patients with chronic hepatitis - 39.2±1.58 pg/ml, $p<0.05$, which indicates more severe changes in the cytokine profile, most likely due to the previous covid infection. The susceptibility of the gastrointestinal tract to SARS-CoV-2 infection may be due to the presence of angiotensin-converting enzyme receptors. The viral nucleocapsid protein was found in the cytoplasm of epithelial cells of the stomach, duodenum and rectum. Understanding of the pathogenesis of digestive diseases associated with the SARS-CoV-2 virus is expanding, but its impact on existing chronic gastrointestinal diseases remains unclear.




Rice. 2 Indicators of interferon status in patients with chronic hepatitis + Covid19 and liver cirrhosis.

The incidence of liver damage in patients with COVID-19, according to various studies, varies from 14 to 53% [18]. The mechanisms of direct effects of the SARS-CoV-2 virus on the liver (direct cytotoxicity due to active replication of the virus in liver cells) are not well understood. In earlier studies related to infection with coronaviruses of the Betacoronavirus genus (SARS-CoV (2002–2003) and MERS-CoV (2012)), liver damage was quite common and associated with disease severity [19].

As is known, SARS-CoV, as well as SARS-CoV-2, use ACE2 as receptors for entry into cells, which are widely distributed in the cells of the heart, kidneys, blood vessels, especially alveolar epithelial cells, as well as the liver, pancreas, intestinal epithelium, which ensures systemic damage [4]. However, it is not entirely clear

whether liver damage can be caused directly by the SARS-CoV-2 coronavirus. Previous RNA-seq sequencing data in the Human Protein Atlas database support ACE2 expression in SARS-CoV liver [10]. Moreover, a low frequency of ACE2 expression is observed only in cholangiocytes, but not in hepatocytes, Kupffer cells or endothelial cells. In addition, SARS-CoV, through the specific protein 7a, is capable of inducing apoptosis in cell lines of various organs (including lungs, kidneys, liver) in a caspase-dependent manner.

This indicates the possibility of direct effects of SARS-CoV on liver tissue. Immune-mediated liver injury may be associated with macrophage activation syndrome, in the context of a hyperinflammatory syndrome characterized by a cytokine storm of COVID-19-associated coagulopathy and multiple organ failure within the framework of severe and extremely severe COVID-19 [9].

**Conclusions**

1. Patients suffering from chronic hepatitis who have suffered from Covid 19 are characterized by suppressed secretion of IgG, IgA, increased levels of IgM, IFN α, IFN γ, and the level of IgM and IFN α was higher compared to patients with liver cirrhosis.
2. For patients suffering from liver cirrhosis, a decrease in the secretion of IgG, IgA, an increase in the level of IgM, IFN α, IFN γ was detected, and the level of IFN γ was higher in comparison with patients suffering from chronic hepatitis who had Covid 19.
3. All patients who have had Covid-19 require further observation to assess long-term consequences.

**Bibliography:**


1. Wang J, Ni H, Chen L, Song WQ. Interleukin-10 promoter polymorphisms in patients with hepatitis B virus infection or hepatocellular carcinoma in Chinese Han ethnic population. //Hepatobiliary Pancreat Dis Int. – 2006. – 5(60). P. 4.
2. Wang X. et al. High-mobility group box 1 (HMGB1) -toll-like receptor (TLR) 4-interleukin (IL)-23-IL-17A axis in drug-induced damage-associated lethal hepatitis: Interaction of γδ T cells with macrophages. //Hepatology. — 2013. — 57(1) — P. 373-384.
3. Wang, S., Huang, D., Sun, S., Ma, W., & Zhen, Q. Interleukin-10 promoter polymorphism predicts initial response of chronic hepatitis B to interferon alpha. //Virology journal. — 2011 — 8.(28) — P. 422.
4. ПАТТАХОВА, М., & МУТАЛОВ, С. (2022). *Жигарнинг дори-дармонлар таъсирида зарарланиши* (Doctoral dissertation, Узбекистан, Ташкент).
5. Салаева, Д. Т., Зуфаров, П. С., & Якубов, А. В. (2008). Сравнительная оценка влияния ингибиторов протонной помпы на некоторые механизмы цитозащиты при экспериментальной гастропатии. *Современные наукоемкие технологии*, (3), 63-63.
6. Зокирхужаев, Ш. Я., Рустамова, М. Т., Паттахова, М. Х., Нарзиев, Н. М., Жалолов, Н. Н., & Муталов, С. Б. (2023). Коронавирус инфекцияси ва жигар зарарланиши.
7. Зокирхўжаев, Ш. Я., Рустамова, М. Т., Паттахова, М. Х., Жалолов, Н. Н., & Муталов, С. Б. (2023). Сурункали жигар касалликларида соғлом овқатланишнинг аҳамияти.
8. Паттахова, М. Х., & Муталов, С. Б. (2022). Хронические заболевания печени и особенности гуморальных факторов.
9. Якубов, А. В., & Паттахова, М. Х. (2009). Влияние компонентов и некоторых схем противоязвенной терапии на регенераторные процессы в слизистой ткани желудка при экспериментальной язве. *Фундаментальные исследования*, (7), 57-61.
10. Паттахова, М. Х., Якубов, А. В., & Саидова, Ш. А. (2008). Эффективность некоторых производных нитроимидазола на ферментативные механизмы цитозащиты в слизистой желудка при экспериментальной язве. *Современные наукоемкие технологии*, (3), 61-61.

11. Зокирхўжаев, Ш. Я., & Паттахова, М. Х. (2022). Clinical Features and Lab Values of Patients with Chronic Hepatitis after Covid-19.
12. Закирходжаев, Ш. Я., & Паттахова, М. Х. (2023). Анализ рациона питания больных при заболеваниях печени после перенесенного Covid-19.
13. Закирходжаев, Ш. Я., & Паттахова, М. Х. (2023). Коррекция диетического питания пациентов с заболеваниями печени после перенесенного Covid-19 с применением местных продуктов.
14. Зокирхужаев, Ш. Я., & Толибжонова, М. Х. (2024). ОЦЕНКА ПИТАНИЯ ПАЦИЕНТОВ С ХРОНИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ ПЕЧЕНИ И ИХ ДИЕТИЧЕСКАЯ КОРРЕКЦИЯ.
15. Зокирхўжаев, Ш. Я., Паттахова, М. Х., & Муталов, С. Б. (2024). ТАЛАБАЛАР БИЛАН ЎҚУВ МАШҒУЛОТЛАРИНИ ЎТКАЗИШДА СУҲБАТ КЎРИНИШИДАГИ МАЪРУЗА УСУЛИДАН ФОЙДАЛАНИШ.
16. Паттахова, М. (2021). Изучение пищевого статуса пациентов с хроническими заболеваниями печени.
17. Зокирхужаев, Ш. Я., & Толибжонова, М. Х. (2024). Изучение пищевого статуса пациентов с хроническими гепатитами.
18. Rahimov, B. B., Salomova, F. I., Jalolov, N. N., Sultonov, E. Y., & Obloqulov, A. G. (2023). O 'ZBEKISTON RESPUBLIKASI NAVOIY SHAHRI HAVO SIFATINI BAHOLASH: MUAMMOLAR VA YECHIM YOLLARI.
19. Jalolov, N. N., Sultonov, E. Y., Imamova, A. O., & Oblokulov, A. G. (2023). Main factors of overweight and obesity in children. *Science Promotion*, *1*(2), 2-4.
20. Kobiljonova, S., Sultonov, E., Sultonova, D., Oblokulov, A., & Jalolov, N. (2023). CLINICAL MANIFESTATIONS OF GASTROINTESTINAL FOOD ALLERGY. *Евразийский журнал медицинских и естественных наук*, *3*(5), 142-148.
21. Sadullayeva, X. A., Salomova, F. I., & Sultonov, E. Y. (2023). OCHIQ SUV HAVZALARI MUHOFAZALASH OB'EKTI SIFATIDA. V МЕЖДУНАРОДНАЯ НАУЧНО-ПРАКТИЧЕСКАЯ КОНФЕРЕНЦИЯ «СОВРЕМЕННЫЕ ДОСТИЖЕНИЯ И ПЕРСПЕКТИВЫ РАЗВИТИЯ ОХРАНЫ ЗДОРОВЬЯ НАСЕЛЕНИЯ».
22. Саломова, Ф. И., Рахимов, Б. Б., Султонов, Э. Й., & Облақулов, А. Г. (2023). Навоий шаҳри атмосфера ҳавоси сифатини баҳолаш.
23. Salomova, F., Sadullaeva, K., Samigova, N., & Sadirova, M. (2022). *Study of regional features of dynamics of acute intestinal diseases in the Republic of Karakalpakstan (Livorno, Italy конф.)* (Doctoral dissertation, Livorno, Italy).
24. Косимова, Х. Т., & Садирова, М. К. (2018). ОЦЕНКА ТЯЖЕСТИ И НАПРЯЖЕННОСТИ ТРУДОВОЙ ДЕЯТЕЛЬНОСТИ ВРАЧЕЙ ФИЗИОТЕРАПЕВТИЧЕСКИХ КАБИНЕТОВ. In *WORLD SCIENCE: PROBLEMS AND INNOVATIONS* (pp. 276-278).