

## **Studies on the Determination of Cytokines in Patients with Chronic Hepatitis C with Cryoglobulinemia**

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**Abstract:** 40 patients with CHC with extrahepatic manifestations were included in the conducted studies to determine the cytokines IL-10 and IL-18 in patients with CHC, depending on the presence of cryoglobulinemia. The results of the study showed that in patients with CHC with extrahepatic manifestations, the anti-inflammatory cytokine IL-10 was reduced in patients by 2.37 times, and there was a significant increase in the content of pro-inflammatory cytokine IL-18 in the blood serum by 2.71 times in relation to normal values

**Keywords:** chronic hepatitis C, extrahepatic manifestations, cryoglobulin, interleukin, cytokine.

### **Relevance**

Viral hepatitis ranks first in the list of chronic liver diseases, accounting for 40-60% of the total number of patients with chronic hepatitis. Currently, there are more than 175 million people infected with the hepatitis C virus in the world. The significance of this pathology is due to a high incidence rate, an increase in the number of virus carriers, a change in the age structure of infected people with a predominance of young people, and an increase in the percentage of extrahepatic manifestations. It has been established that the pathogenesis of extrahepatic manifestations in chronic hepatitis C (CHC) is based on various mechanisms: the possibility of hepatitis C virus replication.

In the extrahepatic region, the manifestation of immunocompetent cells - the connection of HCV infection with B-lymphocyte occurs using CD81; heterogeneity of genotypes and frequent mutations of the virus genome due to prolonged presence of the virus in the body; induction of a cascade of immunopathological reactions that will lead to the indication of lipid peroxidation processes in the hepatic parenchyma [1]. It is well known that end-stage liver diseases with HCV lead to cirrhosis and hepatocellular carcinoma [2]. However, chronic HCV infection is known to cause a number of systemic disorders, and these disorders are called extrahepatic manifestations of HCV and cover a wide range of conditions, from clinically insignificant presence of various autoantibodies to vasculitis, skin diseases, kidney damage, lymphoproliferative disorders, diabetes, neurological and neuropsychiatric changes, and other diseases. In 74% of patients with HCV infection, extrahepatic manifestations may appear, which may appear long before the manifestation of liver disease [3,4].

Prolonged stimulation of B-lymphocytes with viral antigens is the cause of mixed cryoglobulinemia [5]. According to detectability data, cryoglobulinemia is observed in 42-96% of patients. [6, 7]. In these patients гепатита, 70-86% of hepatitis C virus RNA is detected in the blood serum, 93-99% is observed in cryoprecipitates, and the concentration of hepatitis C RNA is tens of thousands of times higher in cryoprecipitates than in blood serum [8,9,10]. The main

mediators of the inflammatory process are cytokines, which are responsible for the formation of specific immunity and provide information about the natural elimination of the hepatitis C virus [11, 12]. Manifestations of polymorphic cytokine genes, as well as their promoters, can lead to changes in the level of expression of the genes of inflammatory mediators themselves, to modification of the final product, and thereby affect the immune response [13]. The chronic process of infectious genesis develops with the production of polymorphic cytokine genes, long-term persistence of the virus, and resistance to antiviral therapy observed in chronic hepatitis C [14, 15]. In the initial stages of HCV infection, proinflammatory cytokines, which are involved in triggering a specific immune response, are of primary importance and the effector stage of immunity [16]. Deposition and replication of the HCV virus occurs in monocytes, T- and B-lymphocytes, which proves the hepatotropy of the virus. [17]. It is established that in the development of extrahepatic. The persistence of the virus and its association with cells of the immune system, which lead to various disorders, plays a role in complications of CHC. Thus, questions concerning the role of the immune system in the progression of pathology, the development of extrahepatic manifestations, as well as questions regarding the effect of cryoglobulinemia on cytokine status remain open.

**Objective:** to analyze the results of a study on the determination of cytokines in patients with chronic hepatitis c, depending on the presence of cryoglobulinemia.

### **Material and methods**

Clinical observations, laboratory and instrumental examinations of patients with CHC with extrahepatic manifestations were performed during 2018-2021 on the basis of the Bukhara Infectious Diseases Hospital. 120 patients with chronic viral hepatitis were examined, including 52 patients with extrahepatic manifestations (the main group) and 68 patients with chronic viral hepatitis C without extrahepatic manifestations (the comparison group). In addition, 25 healthy individuals (a control group) were examined at the age of less than 70 years.

The diagnosis of CHC in patients was established on the basis of epidemiological history, clinical data, and laboratory and instrumental diagnostics.

Hematological parameters were studied using an automatic hematology analyzer BC-20S Mindray (China) that determines the number of white blood cells (WBC), lymphocytes (LYM), monocytes (MID), hemoglobin (HGB), red blood cells (RBC), platelets (PLT), as well as the erythrocyte sedimentation rate (ESR) of peripheral blood.

Biochemical parameters of the blood test: total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, glucose (GLU), urea, creatinine were determined using an automatic biochemical analyzer MINDRAY VS-30 (China).

Etiological verification of hepatitis was performed by serological methods of ELISA using the MINDRAY 96 A device (China). CRP was determined using an automatic biochemical analyzer MINDRAY BC-30 (China). For our scientific work, qualitative, quantitative analysis for hepatitis C virus (HCV RNA) and genotyping of the virus by PCR diagnostics was determined using DTlite 4 (RF).

The concentration of pro-inflammatory IL-18 and anti-inflammatory IL-10 in blood serum was determined by solid-phase ELISA using test systems of JSC Vector-Best (Novosibirsk, Russia), in accordance with the manufacturer's recommendations.

### **Results and discussions**

40 patients with CHC with extrahepatic manifestations were involved in the conducted studies to determine the cytokines IL-10 and IL-18 in patients with CHC, depending on the presence of cryoglobulinemia, who were divided into three groups representative by gender and age: (Fig. 1).

Group 1-examined adult patients with CHC with extrahepatic manifestations without cryoglobulinemia (n=20).

Group 2-examined adult patients with CHC with extrahepatic manifestations with cryoglobulinemia (n=20).

The control group consisted of practically healthy individuals with a history of unverified HCV (n=25).

The results obtained for determining the quantitative content of IL-10 showed that this cytokine in normal healthy individuals was  $18.61 \pm 1.02$  pg / ml, which is 2.37 times statistically significantly more than in the examined patients -  $7.86 \pm 0.92$  pg / ml ( $P < 0.001$ ). A decrease in the concentration of this anti-inflammatory cytokine in the blood serum indicates a decrease in anti-infective (antiviral) protection in the subjects patients.

Further studies were conducted on the effect of cryoglobulinemia on the detection of IL-10 in blood serum in adult patients with chronic hepatitis C with extrahepatic manifestations. The results of studies show that in this category of patients with cryoglobulinemia, the concentration of IL-10 increases (up to  $9.42 \pm 0.99$  pg / ml), compared to patients without cryoglobulinemia by 1.50 times ( $6.29 \pm 0.84$  pg / ml,  $P < 0.05$ ) - Fig.

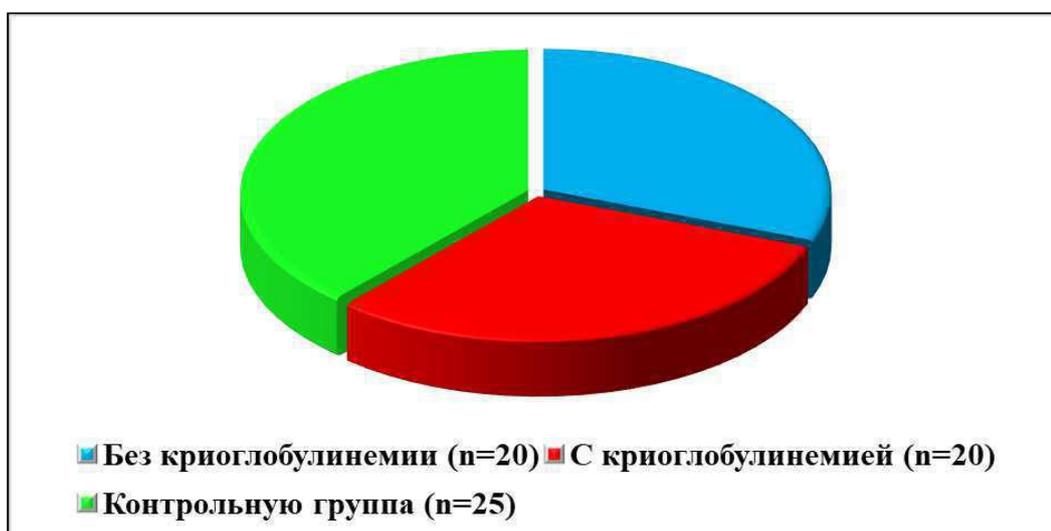
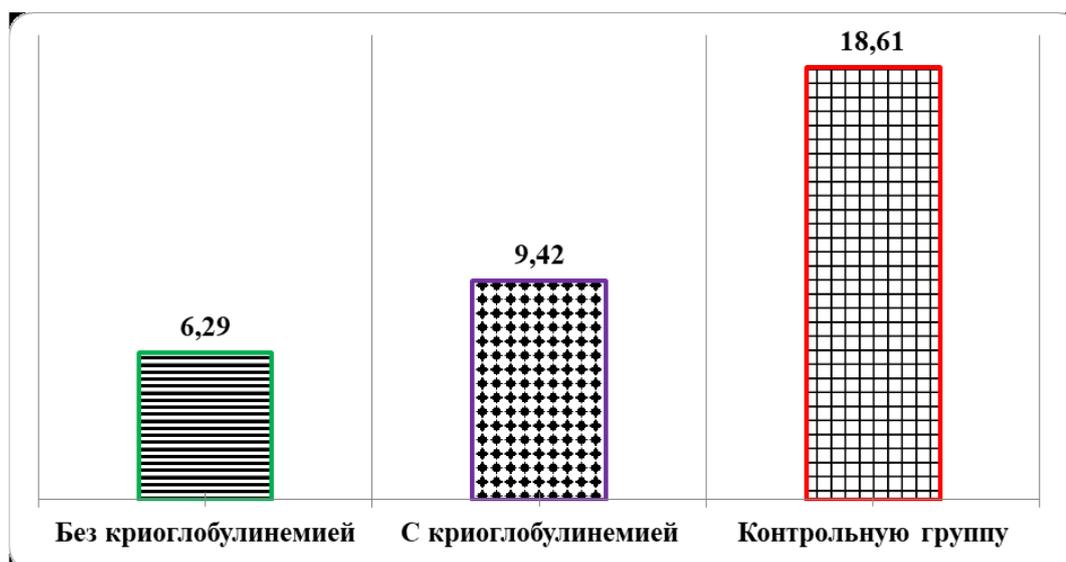


Figure 1 Distribution of the examined patients with CHC and healthy individuals by study groups, absolute numbers.

Rice.



2 Parameters of IL-10 detectability in serum in patients with CHC with extrahepatic manifestations in patients with and without cryoglobulinemia, pg / ml.

Both parameters obtained were 1.98 and 2.96 times lower ( $P < 0.001$ ), respectively, than the level of this cytokine in the blood serum of healthy individuals ( $18.61 \pm 1.02$  pg / ml). The established fact indicates that the presence of cryoglobulinemia has a certain effect on the quantitative content of IL-10 in the blood serum of the examined patients, expressed in the form of a decrease in the increase in the content of this cytokine.

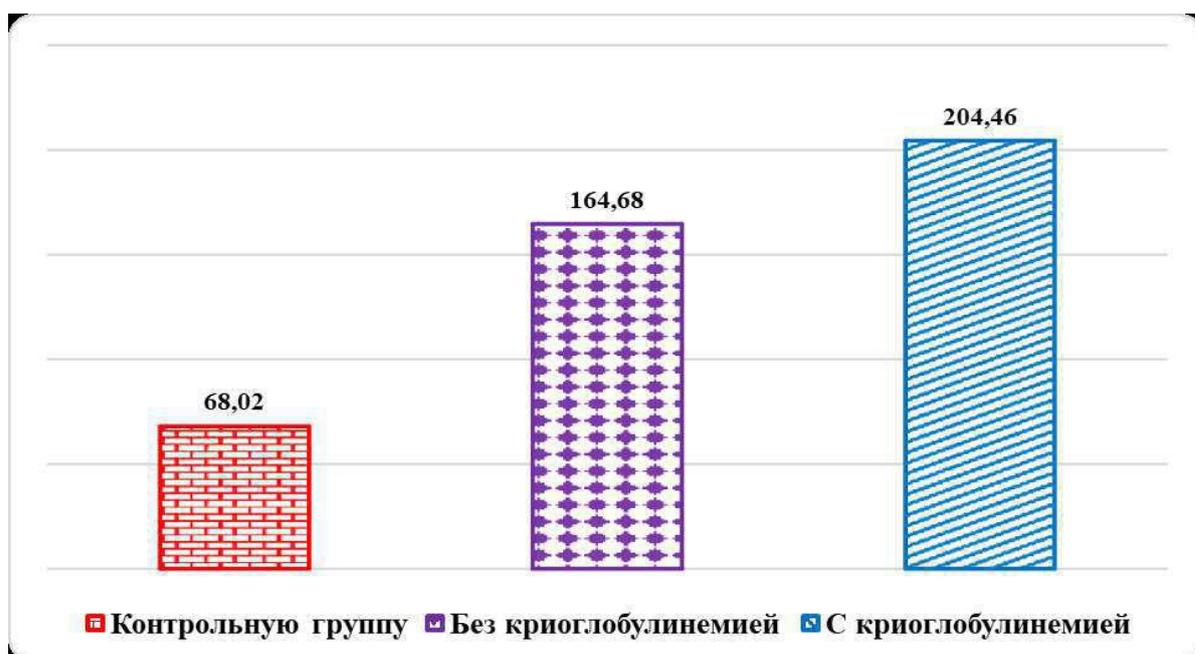
Thus, in patients with CHC with extrahepatic manifestations, the anti-inflammatory cytokine IL-10 was reduced in patients by 2.37 times in relation to the data of healthy individuals. In patients with cryoglobulinemia, this parameter was reduced in relation to the data of healthy individuals (a difference of 1.98 times from the control data,  $P < 0.001$ ), and in patients without cryoglobulinemia

The level of IL-10 was reduced even more, the difference from normal values reached up to 2.96 times ( $P < 0.001$ ). There was also a difference in the content of IL-10 in patients with chronic hepatitis C with extrahepatic manifestations with and without cryoglobulinemia - 1.50 times in favor of patients with cryoglobulinemia ( $P < 0.05$ ). At the next stage of research, the proinflammatory cytokine IL-18 was determined in the same category of patients, depending on the presence of cryoglobulinemia in the body.

Studies have established that in healthy individuals (control group) IL-18 was  $68.02 \pm 2.30$  pg / ml, and in patients with chronic hepatitis C with extrahepatic manifestations, the quantitative content of this cytokine in the blood serum was  $184.57 \pm 14.42$  pg / ml, which is 2.71 times higher than the control values ( $P < 0.001$ ). As can be seen, the decrease in IL-10 and increase in IL-18 in relation to the data of the control group in patients with chronic hepatitis C with extrahepatic manifestations are inversely proportional to each other, which indicates their functions in the body of the studied patients. In addition, the content of IL-18 in the blood serum of patients with CHC with extrahepatic manifestations was studied depending on the presence of cryoglobulinemia, the results of which are shown in Figure 3.3.

It was found that the presence of cryoglobulinemia is accompanied by an increased content of this cytokine compared to the results of patients without cryoglobulinemia. This is proved by the fact that cryoglobulinemia supports the inflammatory process in the body of patients with CHC with extrahepatic manifestations. Thus, in patients with chronic hepatitis C with extrahepatic manifestations, there is a significant increase in the content of proinflammatory cytokine IL-18 in blood serum by 2.71 times compared with normal values (in addition, the effect of the presence of cryoglobulinemia on the content of IL-18 in the blood serum of this category of patients was studied: in patients with cryoglobulinemia, the concentration of IL-18b was increased by 1.24 times in relation to patients without cryoglobulinemia ( $P < 0.05$ ). For the first time, the effect of this phenomenon on the content of the proinflammatory cytokine IL-18 in the blood serum of this category of examined patients was proved.

**Figure 3.3**



### **3. Parameters of IL-18 detectability in the blood serum of patients with CHC with extrahepatic manifestations with and without cryoglobulinemia, pg/ml.**

The results obtained show that the proinflammatory cytokine IL-18 tended to increase significantly in the blood serum relative to the control ( $P < 0.001$ ). In patients without cryoglobulinemia, the content of IL-18 was  $164.68 \pm 12.20$  pg / ml, which is 2.42 times higher compared to the control ( $P < 0.001$ ), and in patients with cryoglobulinemia, the content of this cytokine increased even more, amounting to  $204.46 \pm 16.64$  pg / ml, which is 3.01 times higher compared to normal value ( $P < 0.001$ ). It is interesting to note that the content of IL-18 in the blood serum of CHC patients with extrahepatic manifestations with cryoglobulinemia was significantly increased in relation to patients without cryoglobulinemia by 1.24 times ( $P < 0.05$ ).

This fact indicates that the presence of cryoglobulinemia affects the quantitative content of IL-18 in the blood serum of patients, in addition, the presence of cryoglobulinemia increases the concentration of cytokines, which indicates a negative effect of this phenomenon on the anti-infective protection of the body.

Comparative analysis convincingly proves the effect of cryoglobulinemia on the content of both studied cytokines in the blood serum, thereby proving the maintenance of the inflammatory process in the body of patients.

This proven fact indicates that cryoglobulinemia has diagnostic value in CHC with extrahepatic manifestations, and also allows us to take a new look at the pathogenesis of this pathology and the treatment tactics of these patients. Thus, in patients with chronic hepatitis C with extrahepatic manifestations, there is a significant increase in the content of pro-inflammatory cytokine IL-18 by 2.71 times in relation to normal values, in addition, the effect of cryoglobulinemia on the content of IL-18 in the blood serum of this category of patients is noted, the difference between the groups was 1.24 times in favor of patients with the presence of the phenomenon. The effect of cryoglobulinemia on the content of proinflammatory cytokine IL-18 in the blood serum of the examined patients was proved. In the presence of cryoglobulinemia both interleukins-IL-18 and IL-10 - were elevated relative to the data of patients without cryoglobulinemia.

### **Conclusions**

The study and analysis of the results of the content of pro-and anti-inflammatory cytokines in patients with chronic hepatitis C with extrahepatic manifestations revealed the following patterns:

first, in patients with CHC with extrahepatic manifestations, the anti-inflammatory cytokine IL-10 was reduced in the blood serum by 2.37 times, and the pro-inflammatory cytokine IL-18 was increased by 2.71 times relative to normal values ( $P < 0.001$ ), which indicates a strain in the immune system of patients with this pathology;

secondly, in patients with CHC with extrahepatic manifestations with cryoglobulinemia, IL-10 was 1.50 times higher, IL-18 1.24 times higher in relation to patients without cryoglobulinemia;

third, the effect of cryoglobulinemia on the content of anti-inflammatory cytokine IL-10 and pro-inflammatory cytokine IL-18 in the blood serum of patients was proved for the first time, thereby revealing that cryoglobulinemia leads to a decrease in the anti-infective protection of the body of these patients;

Fourth, the diagnostic value of cryoglobulinemia in CHC with extrahepatic manifestations was proved, which allowed us to take a new look at the pathogenesis of this pathology and the treatment tactics of these patients.

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