Mixed cryoglobulinemia is the most common extrahepatic manifestation of chronic HCV-infection. Cryoglobulinemic syndrome characterized by typical clinical triad (skin purple, severe weakness, arthralgia) and possible multiple organ lesions. In chronic HCV-infection imbalance of pro- and anti-inflammatory cytokines is established with advantage of anti-inflammatory cytokines. This imbalance increases in case of severe liver fibrosis. The question of the role of cytokines in chronic HCV-infection with mixed cryoglobulinemia is controversial. It is difficult question about features of liver injury in patients with mixed cryoglobulinemia.

Materials and methods. The study involved 82 patients with chronic hepatitis C age between 20 and 59 years. Etiological diagnosis is confirmed by detection anti-HCV in serum by ELISA, HCV-RNA by polymerase chain reaction. Stage liver fibrosis was determined by morphological study of hepatobioptats. The content of interferon-γ and interleukin-4 in serum were determined by ELISA. Cryoglobulins content in blood serum determined by spectrophotometric method. Depending on the availability of cryoglobulins patients were divided into groups: I group - 64 patients with mixed cryoglobulinemia (main group), II group - 18 patients without cryoglobulinemia (comparison group).

Results. The majority (51 – 79,7%) patients with chronic hepatitis C patients with mixed cryoglobulinemia had clinical manifestations of mixed cryoglobulinemia: weakness - in 48 (75%) patients, arthralgia - in 23 (35,9%) patients, skin purpura - in 19 (29,7%), angiospastic stage Raynaud's syndrome - in (14,1%), signs of peripheral sensory polyneuropathy - in 18 (28,1%) patients, signs of kidney damage - in 1 (1,6%) patients.

Patients with mixed cryoglobulinemia had lowest content of interferon-γ and highest content of interleukin-4 in serum compared with healthy individuals. In addition, the content of interleukin-4 in patients with mixed cryoglobulinemia was the highest (p <0,05) compared not only with healthy people, but with patients of II group. Correlation between the concentration of cryoglobulins and content of interferon-γ (r = - 0,32, p <0,05) and interleukin-4 (r = 0,36, p <0,05) was registered.

Among patients with chronic hepatitis C different stages of liver fibrosis were registered: F1 was detected in 8 (26,7%), F2 - 8 (26,7%), F3 - 6 (20,0%), F4 - in 8 (26,7%) patients. Patients with fibrosis stages F 3-4 had significantly higher (p <0,05) level of mixed cryoglobulins in the serum compared to patients with liver fibrosis F 1-2. Patients with liver fibrosis stages F 3-4 had greater frequency of clinical signs of cryoglobulinemia syndrome,
compared to patients with liver fibrosis stages F 1-2. So, in patients with liver fibrosis F 3-4 more expressed general weakness (100 vs 62.5%, $\chi^2 = 6.56$, p <0.05), the presence of skin purpura (at 71.4 against 12.5%, $\chi^2 = 12.9$, p <0.01), the development of Meltzer triad (at 42.8 versus 6.3%, $\chi^2 = 5.23$, p <0.05) were registered. Increase of mixed cryoglobulins in serum is associated with appearance of signs cryoglobulinemia syndrome (severe general weakness ($r = +0.42$, p <0.05), skin purpura ($r = +0.33$, p <0.05) and syndrome Reynaud ($r = +0.33$, p <0.05)), the number of signs cryoglobulinemia syndrome ($r = +0.59$, p <0.01) and severity of liver fibrosis ($r = +0.36$, p <0.05).

Increase of interleukin-4 is associated with the appearance of clinical manifestations of cryoglobulinemia syndrome (general weakness ($r = +0.32$, p <0.05), skin purpura ($r = +0.38$, p <0.05) and severe liver fibrosis ($r = +0.89$, p <0.01).

**Conclusions.** 1. Increase of mixed cryoglobulins in serum is associated not only with the appearance of some signs of cryoglobulinemia syndrome, including severe general weakness ($r = +0.42$, p <0.05), skin purpura ($r = +0.33$, p <0.05) and Raynaud's syndrome ($r = +0.33$, p <0.05), but also with the number of signs of cryoglobulinemia syndrome ($r = +0.59$, p <0.01) and severity of liver fibrosis ($r = 0.36$, p <0.05).

2. In patients with chronic hepatitis C with mixed cryoglobulinemia high content of interleukin-4 (49.3%, p <0.05), which correlates with the concentration kriohlobuliniv ($r = +0.36$, p <0.05) associated with the emergence of general weak ($r = +0.32$, p <0.05), skin purpura ($r = +0.38$, p <0.05) and the development of liver fibrosis degree F 3-4 ($r = +0.89$, p <0.01).

3. To improve the quality of diagnosis course of chronic hepatitis C it is advisable to determine the quantitative content of cryoglobulin and interleukin-4 in serum, because increased level of cryoglobulins and interleukin-4 in serum is associated with progressive of liver fibrosis and with the risk of clinical manifestation of cryoglobulinemia syndrome.