

Received: 20.11.2022

Accepted: 29.11.2022

Published: 20.12.2022

UDC 616.36-002-036.12+616.72

## CLINICAL FEATURES OF THE COURSE OF ASSOCIATED ARTHRITIS WITH HCV INFECTION AND THE ROLE OF CYTOKINES IN DIAGNOSTICS

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### Resume

Currently, more than a dozen pathologies associated with HCV have been described, including lesions of the joints, muscles, circulatory system, salivary glands, eyes, pancreas, nervous system, kidneys, etc.. HCV is much more than a simple liver infection. Extrahepatic manifestations are clinically apparent in approximately 40-70% of patients and may involve many organs. These mainly include joint disorders (arthritis or arthralgia), mixed cryoglobulinemia, small and medium vessel vasculitis, glomerulonephritis, lichen planus, B-cell lymphoma, and cutaneous porphyria. Currently, great importance is attached to the diagnosis of HCVaA. Non-invasive diagnostic methods are most effective for determining the early stage of the disease, so the formation of a target group at risk of developing HCVaA using reliable biomarkers of extrahepatic manifestations of hepatitis is a priority. Recently, the management of patients with HCVaA has been actively studied. However, in our country, there are few scientific works devoted to the study of the prevalence, diagnosis and treatment of HCV-associated rheumatic manifestations. This work was aimed at assessing the frequency of detection of arthritis in patients infected with HCV (HCVaA), as well as to analyze the identified features of its manifestations using clinical research methods in this category of patients.

**Key words:** HCV associated arthritis, chronic hepatitis C, cryoglobulinemia, interleukin 6.

## HCV INFEKTSIYASI BILAN BOG'LIQ ARTRIT KECHISHINING KLINIK XUSUSIYATLARI VA DIAGNOSTIKASIDA SITOKINLARNING AHAMIYATI

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### Rezyume

Hozirgi vaqtda HCV bilan bog'liq o'ndan ortiq patologiyalar, jumladan bo'g'imlar, mushaklar, qon aylanish tizimi, so'lak bezlari, ko'zlar, oshqozon osti bezi, asab tizimi, buyraklar va boshqalarning shikastlanishi tasvirlangan. HCV oddiy jigar infeksiyasigina emas. HCV ning jigargan tashqari klinik ko'rinishlari bemorlarning taxminan 40-70 foizida kuzatiladi va bu bir qator organlarni qamrab oladi. Bularga asosan bo'g'imlarning shikastlanishi (artrit yoki artralgiya), aralash krioglobulinemiya, kichik va o'rta kalibrdagi qon-tomirlar vaskuliti, glomerulonefrit, B-hujayrali limfoma va teri porfiriya kabilari kiradi. Hozirgi vaqtda HCVaA diagnostikasiga katta ahamiyat berilmoqda. Invaziv bo'lmagan diagnostika usullari kasallikning dastlabki bosqichini aniqlash uchun eng samarali hisoblanadi, shuning uchun gepatitning jihardan tashqari klinik ko'rinishlarining ishonchli biomarkerlari yordamida HCVaA rivojlanish xavfi ostida bo'lgan maqsadli guruhni shakllantirish ustuvor hisoblanadi. Yaqinda HCVaA bilan kasallangan bemorlarni boshqarish faol o'rganildi. Biroq, bizning mamlakatimizda HCV bilan bog'liq revmatik ko'rinishlarning tarqalishi, diagnostikasi va davolashni o'rganishga bag'ishlangan ilmiy ishlar kam. Ushbu ish HCV bilan assotsiirlangan artrit (HCVaA) bilan

*kasallangan bemorlarda artriti uchrasht tezligini baholashga, shuningdek ushbu toifadagi bemorlarda klinik tadqiqot usullari yordamida uning namoyon bo'lishining aniqlangan xususiyatlarini tahlil qilishga qaratilgan edi.*

*Kalit so'zlar: HCV bilan bog'liq artrit, surunkali gepatit C, krioglobulinemiya, interleykin 6*

## ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ АРТРИТА, АССОЦИИРОВАННОГО С ВГС-ИНФЕКЦИЕЙ И ЗНАЧЕНИЕ ЦИТОКИНОВ В ДИАГНОСТИКЕ

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### Резюме

*В настоящее время описано более десятка патологий, связанных с ВГС, включая поражения суставов, мышц, системы кровообращения, слюнных желез, глаз, поджелудочной железы, нервной системы, почек и т.д. ВГС - это гораздо больше, чем простая инфекция печени. Внепеченочные проявления клинически проявляются примерно у 40-70% пациентов и могут затрагивать многие органы. К ним в основном относятся заболевания суставов (артрит или артралгия), смешанная криоглобулинемия, васкулит мелких и средних сосудов, гломерулонефрит, красный плоский лишай, В-клеточная лимфома и кожная порфирия. В настоящее время большое значение придается диагностике HCVaA. Неинвазивные методы диагностики наиболее эффективны для определения ранней стадии заболевания, поэтому формирование целевой группы риска развития HCVaA с использованием надежных биомаркеров внепеченочных проявлений гепатита является приоритетной задачей. В последнее время активно изучается ведение пациентов с HCVaA. Однако в нашей стране существует мало научных работ, посвященных изучению распространенности, диагностике и лечению ревматических проявлений, ассоциированных с ВГС. Данная работа была направлена на оценку частоты выявления артрита у пациентов, инфицированных HCV (HCVaA), а также на анализ выявленных особенностей его проявлений с использованием клинических методов исследования у данной категории пациентов.*

*Ключевые слова: ВГС-ассоциированный артрит, хронический гепатит C, криоглобулинемия, интерлейкин – 6.*

### Relevance

Hepatitis C virus (HCV) infection is one of the most difficult health problems, given its high prevalence worldwide and frequent liver diseases and extrahepatic manifestations (HCV-EHM) [1-6]. In terms of morbidity and mortality, HCV-infected people are at risk of serious liver complications, i.e. cirrhosis and liver cancer [7], and less often HCV-EHM. HCV-EHM can be, on the one hand, the result of a violation of the regulation of the immune system due to HCV lymphotropism [6, 8] responsible for various autoimmune and/or lymphoproliferative disorders that can seriously affect the general condition of patients [9-11]. On the other hand, the chronic inflammatory status associated with HCV infection probably explains the cardio-metabolic complications as well as neurocognitive disorders. Individual HCV-EHM are characterized by a widely varying distribution

among groups of patients from different countries [1-6]. Moreover, the percentage of patients with at least one HCV-EHM may increase during the natural course of HCV infection [10,11]. However, the actual incidence of HCV-EHM is not systematically investigated worldwide, probably due to their insidious, often subclinical course and mainly due to the lack of a unified diagnostic approach. As a consequence, the overall incidence of HCV-EHM may be underestimated or in some cases completely missed. This work is an attempt to develop a wide range of diagnostic recommendations for patients with HCV-EHM based on international and own experiences.

Extrahepatic manifestations of HCV can manifest either as organ-specific disorders, i.e. arthritis, neuropathy, glomerulonephritis, etc., or as a systemic autoimmune disorder, as mixed

cryoglobulinemia syndrome (MCGE). Isolated and completely asymptomatic serum cryoglobulins, as a rule, are detected in more than 50% of HCV-infected people, while classical HCG can be diagnosed in 15% of cryoglobulin-positive patients based on both serological (circulating mixed cryoglobulins) and typical clinical and pathological features.

HCV is able to affect B lymphocytes through the CD8 1 receptor, which induces polyclonal activation of B cells, which leads to the production of cryoglobulins (CG), rheumatoid factor (RF) and a number of autoantibodies [19]. The Italian group obtained the same results in one of 4 patients with rheumatoid arthritis (RA) with concomitant HCV infection.

KG products are strictly related to HCV. The prevalence of HCV antibodies in individuals with mixed cryoglobulinemia (MCGE) (II, II-III and III types of cryoglobulinemia) varies from 40 to 90% in different regions [21]. The largest amount of HCV RNA is contained in the cryoprecipitate. Lymphocytes of cryoglobulin-producing patients have the property of concentrating higher amounts of HCV particles on their surface [22]. This event may play a role in the pathogenesis of the disease. In conditions of high prevalence and increasing incidence of HCV, low availability of antiviral therapy, an increase in the number of extrahepatic lesions that occur in about half of patients should be expected.

The pathological processes underlying extrahepatic manifestations are insufficiently studied. The most common extrahepatic manifestation of HCV infection is joint damage. Cacoub and co-authors reported that 23% of the 1,614 patients with chronic hepatitis C, in general, suffered from arthralgia. However, asymptomatic joint damage seems to be much more common. Iagnocco et al. It was found that 96,5% of 29 patients with HCV without joint symptoms had minor inflammatory changes in the knee, hip or shoulder joints during ultrasound examination—a highly sensitive method of joint examination. However, other joints were not examined. Based on this observation and studies reporting arthritis in only 4-5% or less of HCV patients, it can be assumed that these small percentages represent only the tip of the iceberg of general joint inflammation associated with HCV. In any case, it should be emphasized that some clinical reports concerning extrahepatic manifestations of HCV infection were made by non-rheumatologists who could have mistakenly diagnosed milder forms of arthritis with

arthralgias. The clinical picture of HCV-associated arthritis (HCVaA) has been outlined based on several studies. Other studies have shown that the prevalence of joint syndrome associated with hepatitis C virus (HCVaA) is about 4% of patients with HCV. This is a small percentage, because many patients are diagnosed with a joint event only after consulting with a specialist. Poanta L. et al. undertook a prospective study that provides evidence that 20% of patients infected with HCV will have arthralgia in the first year [12]. Articular manifestations present in HCV patients have been observed to be a type of rheumatoid arthritis or arthritis associated with cryoglobulin deposits. These patients have a high prevalence of positive rheumatoid factor (RF) and therefore can often be misdiagnosed with RA [13].

Recently, the features of the management of patients with HCVaA have become the subject of active study. However, in our country, scientific works devoted to the study of the prevalence and diagnosis of HCV-associated rheumatic manifestations are few.

Thus, this study was aimed at assessing the frequency of detection of arthritis in patients infected with HCV (HCVaA), as well as analyzing the identified features of its manifestations using clinical and laboratory research methods in this category of patients.

These studies were aimed at improving the effectiveness of HCVaA diagnosis, based on the characteristics of cytokine concentrations.

**The aim of the work** is to evaluate the concentrations of pro-inflammatory cytokines (interleukin-6-IL6, tumor necrosis factor alpha - TNF- $\alpha$ ) in the serum of HCVaA patients to assess the diagnostic significance of IL-6, to determine the problems and prospects for the use of non-invasive diagnostic biomarkers, in particular IL-6 and TNF- $\alpha$  in clinical practice in patients with HCVaA.

### Materials and methods

The clinical material that served as the basis for this work includes the results of a survey of 52 patients diagnosed with HCVaA who were treated in the rheumatology department of the 3rd clinic of the Tashkent Medical Academy (TMA), as well as received inpatient treatment in the departments of the clinic of the Research Institute of Epidemiology, Microbiology, Parasitic and Infectious Diseases (RIEMPID) of the Republic of Uzbekistan, for the period 2018 to 2020. All patients were diagnosed with HCV-associated

arthritis (HCVaA). The diagnosis was confirmed by the presence of antibodies to HCV (anti-HCV) and HCV RNA by polymerase chain reaction (PCR). The ratio of men and women is 1,36:1, respectively, that is, 30 men (M) and 22 women (F), mean age 38,54±6,00 years. Distribution of patients with HCVaA by gender In 58% of cases, arthritis occurred in men with HCV. At the same time, 48% of patients were of working age - 30-40 years. During the examination of patients, the

following parameters were taken into account: gender, age, main diagnosis, dynamics of biochemical parameters (at the time of admission and at the end of hospitalization). In parallel, we studied a comparative group, which included 36 patients with chronic hepatitis C without associated arthritis, who were registered with infectious disease doctors at polyclinics of the RIEMPID of the Republic of Uzbekistan (Table 1).

Table 1

Clinical characteristics of patients

Group of surveyed	Number of patients		Gender				Age
			M		F		
	n	%	n	%	n	%	From 25 to 60
Main group - HCVaA	52	100	30	57,7	22	42,3	
Comparison group - HCV without arthritis	36	100	22	61,1	14	38,9	

A diagnostic card was compiled for each patient, including passport data, anamnesis of hepatitis and arthrological syndrome, objective examination data (pain assessment by visual analog scale (VAS) for pain was used in all patients as a one-dimensional tool for assessing the intensity of pain), soreness and swelling in various joints, limitation of the volume of movements in them; skin changes, liver condition, laboratory data: general blood test (GAT), general urine test (GUT); biochemical blood parameters: proteinogram, AlAT, AsAT, bilirubin by fractions, cholesterol (HC), lipid spectrum, blood glucose, thymol test, CR-P, RF, as well as immunological parameters: cryoglobulins, interlekin-6, PCR for HCV RNA; instrumental research methods (ultrasound of the liver, ultrasound of joints, radiography of joints, liver elastography).

The following clinical research methods were used in the work:

- general clinical examination
- assessment of the degree of hepatitis activity
- assessment of the duration of arthralgia
- assessment of the severity of joint pain on the VAS scale
- assessment of joint disorders by ultrasound

Statistical processing of the obtained data was carried out using the program “Statistic 6.0”, Biostat and Excel spreadsheets for Windows XP.

**Results and discussion**

Clinical characteristics of HCV-associated arthritis in patients diagnosed with chronic viral hepatitis C in the study groups:

Among 52 patients who were initially diagnosed with HCVaA, 57,7% were men (gender ratio: 30 men: 22 women), the average age of HCVaA patients was 38,54±6,00 years.

Distribution of HCVaA patients by gender in 58% of cases, arthritis occurred in men with HCV. At the same time, 48% of patients were of working age - 30-40 years (Table 1).

The ratio of men and women, respectively, is 1,36:1, the average age of patients diagnosed with HCVaA (M±a) was 38,54± 6,00 years.

In most of all the surveyed patients (44 patients – 84,6%), the duration of HCV was up to 10 years. At the same time, the distribution of patients in groups with associated arthritis and in the comparison group was approximately the same. In 80,76% (42 patients) of cases, hepatitis occurred without arthritis. Thus, the frequency of HCV with articular manifestation was 19,24%.

As for rheumatic complaints, arthralgia was the most common manifestation for patients with HCV infections (92.3%) and the frequency of rheumatic complaints did not have a statistically significant difference between the groups according to statistical analysis. The mean value of VAS was 6,78±1,42 and patients were distributed as follows:

- VAS 1-3 (mild pain): 9,4% of patients with HCV
- VAS 4-6 (moderate pain): 28,6% of HCV patients
- VAS 7-10 (severe pain): 62% of HCV patients

That is, patients of the main group diagnosed with HCVaA complained of joint pain – 48 (92,3%), swelling in the affected joints – 29 (55,7%), restriction of movement in the joints – 20 (38,4%), stiffness during movement – 17 (32,7%), joint deformity – 4 (7,7%).

In addition, we noted that in 29 (55,7%) patients of the main group, articular manifestation occurred in the form of polyarthritis, in 17 (32,7%) - knee joint oligoarthritis, in 5 (9,6%) - ankle joint oligoarthritis, in 1 (1,9%) - polyarthralgia without signs of inflammatory changes according to ultrasound joints.

In the study group of patients, we observed a correlation between the severity of VAS pain and the duration of rheumatic complaints ( $r=0,51$ ;  $p < 0,05$ ), as well as hepatitis activity ( $r=0,46$ ;  $p < 0,05$ ). At the same time, the pain was stronger in patients with a longer course of hepatitis. In addition, there was a weak direct correlation between the severity of joint pain according to VAS in the main groups and the degree of liver fibrosis according to liver elastography ( $r=0,34$ ;  $p < 0,05$ ). That is, in persons with a more pronounced degree of liver fibrosis, according to elastography, higher rates of joint pain were observed according to VAS.

In our study, we observed that the increase in bilirubin levels: in the main group - in 14

(26,9%) patients, in the comparison group - in 8 (22,2%) patients; AlAT: in the main group - in 45 (86,5%) patients, in the comparison group - in 24 (66,66%) patients; AsAT: in the main group - in 35 (67,3%) patients, in the comparison group - in 24 (66,6%) patients; thymol test: in the main group - in 24 (46,15%) patients, in the comparison group - in 20 (55,55%) patients; decrease in albumin levels: in the main group in the group - in 13 (25%) patients, in the comparison group - in 13 (36,11%) patients. There were no significant differences in other biochemical parameters. Here we found that there was a pronounced direct correlation in the main group of patients with HCV between the degree of hepatitis activity and the indicators of AlAT, AsAT and thymol breakdown; an average direct correlation between the duration of hepatitis disease and the indicators of AlAT, AsAT, between the degree of hepatitis activity and the levels of total bilirubin and thymol breakdown, as well as between the severity of pain in joints according to VAS and the severity of the degree of liver fibrosis with AlAT and AsAT levels; there was a weak correlation between the severity of joint pain according to VAS and the degree of liver fibrosis with total bilirubin levels, thymol breakdown indicators.

An average inverse correlation was observed between the duration of hepatitis disease and albumin levels; a weak inverse correlation was between albumin levels, the degree of hepatitis activity and the severity of joint pain according to VAS (Table 2).

Table 2

The main correlations between the biochemical parameters of the main group of patients with HCV and the duration of hepatitis disease, hepatitis activity, the severity of joint pain according to VAS, the degree of liver fibrosis ( $p < 0,05$ )

Indicator	Total bilirubin	AlAT	AsAT	Albumin	Thymol test
Duration of hepatitis disease	0,364*	0,664**	0,678**	-0,468*	0,442*
The degree of hepatitis activity	0,624**	0,953***	0,871***	-0,623**	0,764***
The severity of pain according to VAS prior treatment	0,446*	0,561**	0,613**	-0,340*	0,522*
Severity of liver fibrosis	0,471*	0,553**	0,576**	-0,511**	0,323*

Note: \* - low correlation dependence; \*\* - average correlation dependence; \*\*\* - strong correlation dependence

We noticed that a relationship has been established between the duration of hepatitis disease, its activity, the severity of liver fibrosis according to elastography and changes in the levels of basic biochemical parameters. That is, the longer hepatitis lasts, its degree of fibrosis was expressed, and the more active it was, the higher the levels of bilirubin, AlAT, AsAT, thymol samples, the more pronounced joint pain in your and albuminemia are expressed. The latter correlates with the parameters of the thymol test.

As the results of the study showed, among patients with CGE, the incidence of articular manifestation was 74,3%. At the same time, patients in the group diagnosed with HCV with articular manifestation showed the frequency of occurrence of CGE – in 29 patients, in the HCV group without articular manifestation - in 10 patients, the total number of patients with CGE - 39 people. The duration of articular manifestation of HCV in the group of patients with CGE was more often up to 5 years, and the duration of rheumatological complaints over 10 years was

less ( $p < 0,05$ ). In 100% of cases, the subjects of both groups were concerned about joint soreness. In 79,3% (23) of patients with CGE arthropathy occurred in the form of polyarthritis ( $p < 0,001$ ), and in patients without it - in 65,2% (15) of observations, oligoarthritis of the knee or ankle joints was detected ( $p < 0,01$ ), and polyarthritis was detected only in 34,7% (8) of people. In (24) 82,7% of patients with CGE, the presence of swelling was noted in the area of several groups of joints, including small joints of the hands and feet ( $p < 0,001$ ), while in patients without CGE only in the knee or ankle joints, and swelling in several groups of joints was detected only in (3) 13,04% of these patients ( $p < 0,001$ ). The presence of stiffness during movement was observed only in the small joints of the hands in patients with CGE in 41.37% (12), and without it only in (2) 8.69% of cases ( $p < 0,01$ ). Movement restriction in several joint groups was observed in 55.1% (16) of people with CGE and only in (3) 13,04% of people without it ( $p < 0,001$ ). Joint deformities were not observed in the examined group ( $p < 0,001$ ).

Table 3  
IL-6, TNF- $\alpha$  and autoantibodies (isotype of rheumatoid factor IgM, IgM -RF) concentrations in the serum of patients with HCVaA and in the control group

Parameter	Levels in the main group		
	HCVaA	control group	p
IL-6 (picograms per milliliter)	29,17 (18,20–40,14) pg / ml	2,73 (2,12–3,34) pg / ml	<0,0001
TNF- $\alpha$ (picograms per milliliter)	52,57 (34,62–70,52) pg / ml	4,35 (3,37–5,31) pg / ml	<0,0001
IgM-RF IU/ml (international unit per milliliter)	42,63 (30,44–54,82) IU/ml	5,19 (3,97–6,41) IU/ml	<0,0001
CR-P Mg/l (milligrams per liter)	14,07 (10,59–17,55) Mg/l	4,87 (3,96–5,79) Mg/l	<0,0001
ESR Mm/h (millimeter per hour)	13,70 (11,12–16,27) Mm/h	11,66 (9,20–14,12) Mm/h	<0,0001

In our study, we observed that in the group with CGE, the duration of hepatitis up to 10 years ( $p < 0,001$ ) was more common, and in the group without CGE - up to 5 years ( $p < 0,05$ ). In patients with CGE, hepatomegaly according to liver ultrasound was found in 86,2% (25), which is significantly more than in the group of patients without CGE - in 17,4% (4) people ( $p < 0,001$ ). According to liver elastography data, signs of liver fibrosis of the 2nd and 3rd degree prevailed in the subjects with CGE - in 44,8% (13) and 38% (11) patients, respectively ( $p < 0,05$ ), relative

to the indicators of the group without CGE, where the 1st and 2nd degrees of fibrosis were more often observed – 39,1% (9) and 34,7% (8) of patients of the corresponding ( $p < 0,05$ ). The highest frequency of extrahepatic manifestations was also observed in the group of patients with CGE – in 17 (58,6%) patients, and in the group without CGE only in 3 (13,04%) patients. In individuals with cryoglobulinemic syndrome, the average number of KG in the blood was determined, the longest duration of hepatitis disease, all these patients had hepatomegaly

according to liver ultrasound and mainly grade 3 liver fibrosis according to liver elastography ( $p < 0,001$ ).

Thus, in individuals with CGE, the articular manifestations of HCV were, in general, more severe, in the form of polyarthritis with the greatest number of painful and swollen joints per 1 person, more pronounced joint pain in VAS compared to the group without CGE.

In our study, we found that the concentrations of anti-inflammatory cytokines IL-6 (29,17 pg/ml, 95%) and TNF- $\alpha$  (57,52 pg/ml, 95%) in the serum of patients in the main group were

higher than in the control group (2,73 pg/ml, 95%  $p < 0,0001$  and 4,35 pg/ml, 95%  $p < 0,0001$ , respectively) (Table 3).

In the study group of patients, we observed statistically significant differences in CR-P concentrations and ESR levels between the main groups and the control group (CRP/control group -  $p < 0,0001$ , ESR/control group -  $p < 0,0001$ ). Comparing the average concentrations of CR-P and ESR between the two groups, we noticed that we have statistically significant differences between the main and comparative groups ( $p < 0,0001$ ).

Table 4

Correlations between IL-6, TNF- $\alpha$  and HCVaA indices

Parameter	IgM-RF	IL-6	TNF- $\alpha$	CR-P	ESR
IgM-RF IU/ml (international unit per milliliter)		$r = 0,578$ $p = 0,003 *$	$r = -0,052$ $p = 0,809$	$r = -0,269$ $p = 0,204$	$r = 0,210$ $p = 0,325$
IL-6 (picograms per milliliter)			$r = -0,154$ $p = 0,471$	$r = -0,101$ $p = 0,640$	$r = 0,298$ $p = 0,158$
TNF- $\alpha$ (picograms per milliliter)				$r = 0,050$ $p = 0,816$	$r = 0,015$ $p = 0,944$
CR-P Mg/l (milligrams per liter)					$r = -0,342$ $p = 0,101$

In the main group, we observe that: IL-6 correlated fairly well with IgM-RF ( $r = 0,578$ ,  $p = 0,003$ ).

Comparison of the studied parameters in the main and comparative groups of patients showed that IL-6 and TNF- $\alpha$  have higher diagnostic usefulness as markers of the disease (Table 4).

In some studies, HCVaA patients showed 64,7% IgM-RF. In 50-70% of cases with RF-positive HCV infection, rheumatic symptoms and signs may be observed. A study conducted by Sene D. et al. It was shown that RF-positivity was about 81% in patients with other rheumatic diseases, whereas in HCVaA this positivity was between 54-82%.

Due to the fact that it is possible to observe similarities both in the prevalence of positive RF in the studied patients with HCVaA and with arthritis of different etiologies, the test should not be used to make a reliable distinction between this current condition and other rheumatic diseases.

According to ultrasound of the joints, synovitis occurred in 46 (88,4%) people ( $p < 0,001$ ). Signs of synovitis of a minor nature were in 24 (52,1%) patients ( $p < 0,001$ ); moderate in 16 (34,7%) and pronounced in 6 (13,04%).

According to the localization of synovitis, the subjects were distributed as follows: 20 (43,47%) - only knee joints, 5 (10,8%) people - only ankle joints, 2 (4,3%) people - only wrist joints and 19 (41,3%) people - several groups of joints, including small joints of the hands and feet.

The presence of signs of bursitis was detected in 11 (21,1%) of the subjects. The main localization of bursitis was: 7 (63,63%) people had knee joints, 4 (36,36%) people had ankle joints.

Erosion of articular surfaces occurred in 4 (7,7%) patients only in small joints of the hands. It is worth noting that the erosions during ultrasound of the joints did not look like true erosions, but "pseudo-erosions". No erosions were detected on the radiography of the joints. This is important to take into account when differential diagnosis between HCVaA and RA.

In conclusion, it should be noted that the incidence of articular manifestations in patients with chronic viral hepatitis C is 19,2%. In patients with cryoglobulinemia, articular manifestations of HCV are 74,3%. HCVaA has an intermittent character, occurs in the form of oligoarthritis mainly of the knee joints or symmetrical polyarthritis involving small joints of the hands and feet. In the presence of

cryoglobulinemia, the articular syndrome proceeds mainly in the form of polyarthritis with more pronounced changes in the joints and periarticular tissues according to ultrasound examination of the joints. In addition, there is a reliable direct relationship between the severity of the articular syndrome in patients with chronic viral hepatitis. With its duration, duration of hepatitis, the degree of its activity, a high level of circulating immune complexes, the degree of synovitis and the presence of periartthritis according to ultrasound examination of the joints.

Based on the obtained clinical data, it was found that patients with HCV with articular syndrome in 92,3% of cases complained of joint pain, less often of swelling in the affected joints – 55,7% of people, restriction of movement in the joints – 38,4% of people, stiffness during movement – 32,7% of people, joint deformity – 7,7% of people. Joint pains were more often of an intermittent nature, were symmetrical and intensified with an increase in the activity of the underlying disease. In both groups, stiffness was observed symmetrically, mainly in the small joints of the hands. At the same time, the duration of stiffness was in the range of 10 to 20 minutes. In most cases, the swelling in the area of the affected joints was symmetrical. In individuals with the presence of this symptom in the area of several groups of joints, it was mainly observed in small joints of the hands and feet. In the group of patients with HCV, 55,7% of people had joint syndrome in the form of polyarthritis, 32,7% had knee joint oligoarthritis, and 9,6% of people had ankle joint oligoarthritis according to joint ultrasound.

It was noted that in the subjects of the study groups there was a correlation between the severity of VAS pain, the duration of joint syndrome and hepatitis activity, while the pain was stronger in patients with a longer course of hepatitis.

Cytokines play a significant role in the immune response to viral agents. Cytokines are known to be key mediators of inflammation and joint destruction in RA [19, 20]. IL-6, known as a pro-inflammatory cytokine, is usually elevated during acute infection and inflammation [21, 22].

Various pro-inflammatory cytokines seem to be activated in chronic HCV infection, and the development of chronic hepatitis C is mainly associated with them. TNF- $\alpha$  is one of the most studied cytokines involved in HCV infection.

The results of our studied cases offer interesting assumptions about the role of cytokines in the pathogenesis of HCV complicated by arthritis. Patients with chronic HCV infection and arthropathy had a higher level of circulating TNF- $\alpha$

compared to patients without articular manifestation ( $p < 0,0001$ ).

We have demonstrated that the concentrations of the studied cytokines (IL-6, TNF- $\alpha$ ) in the blood serum correlate better with HCVaA indicators. The concentrations of both cytokines correlated with each other were not very high. We also observed that IL-6 and TNF- $\alpha$  correlated better with autoantibodies.

When assessing the diagnostic usefulness of IL-6, TNF- $\alpha$  and autoantibodies (IgM-RF), their characteristics in terms of both diagnostic accuracy and the Youden index are comparable to the notion that IL-6 and TNF- $\alpha$  have higher specificity and sensitivity in the group of patients with HCVaA.

For the purpose of differential diagnosis between RA and articular syndrome on the background of HCV having a rheumatoid-like course, data from instrumental examination methods (radiography and ultrasound of joints) were also used. As a rule, in patients with rheumatoid-like course of articular syndrome, no inflammatory changes were observed in the UAC, RF and C-RB were not always positive, the analysis for the presence of ADC was negative, erosive processes in the joints, if present, were of the nature of "pseudo-erosions" according to ultrasound of the joints.

### Conclusions

Based on the results of biochemical studies, the relationship between the duration of hepatitis disease, its activity, the degree of severity of liver fibrosis according to elastography and changes in the levels of basic biochemical parameters has been established. At the same time, the longer hepatitis proceeds and the more active, as well as the more pronounced liver fibrosis was, the higher the levels of bilirubin, AlAT, AsAT, thymol test, the more significant joint pain according to VAS. The latter correlates with the parameters of the thymol test.

We can say that due to the high sensitivity to discrimination /diagnostic accuracy, the determination of serum concentrations of IL-6 and TNF- $\alpha$ , possibly in combination with autoantibodies, may be useful in the diagnosis and distinction of patients with rheumatic disease and HCV patients with articular manifestations and may be useful for monitoring the course of the disease. In the future, in a study that will continue on this issue, we propose to apply this method to another group of patients consisting of more subjects to test this model.

Based on the above, we can say that our study will be useful in the management of patients with HCVaA, monitoring the course of the disease and their diagnosis.

In the future, in a study that will continue on this issue, we propose to apply this method to another group of patients consisting of more subjects to test this model.

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Entered 20.11.2022