MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Sumtsova K, Berezhok V, Lishnevska A, Chemych M. The dependence of changes in laboratory indicators on accompanying pathology in patients with viral hepatitis C. *East Ukr Med J*. 2024;12(1):69-80

DOI: https://doi.org/10.21272/eumj.2024;12(1):69-80

ABSTRACT

Kateryna Sumtsova
https://orcid.org/0009-0004-8410-8672
Department of Infectious Diseases and Epidemiology, Sumy State University, Sumy, Ukraine

Vladyslav Berezhok
https://orcid.org/0009-0004-5102-2629
Department of Infectious Diseases and Epidemiology, Sumy State University, Sumy, Ukraine

Anastasiia Lishnevska
https://orcid.org/0000-0002-3388-1508
Department of Infectious Diseases and Epidemiology, Sumy State University, Sumy, Ukraine

Mykola Chemych
https://orcid.org/0000-0002-7085-5448
Department of Infectious Diseases and Epidemiology, Sumy State University, Sumy, Ukraine

THE DEPENDENCE OF CHANGES IN LABORATORY INDICATORS ON ACCOMPANYING PATHOLOGY IN PATIENTS WITH VIRAL HEPATITIS C

Objective: to determine the dependence of changes in hematological, biochemical indicators and indexes of nonspecific reactivity, inflammation, endogenous intoxication on accompanying pathology in patients with chronic viral hepatitis C (HCV).

Materials and methods: hematological, biochemical, non-specific immunological changes were analyzed in 20 chronic HCV patients without cardiovascular system pathologies, in 20 chronic HCV patients with concomitant coronary heart disease (CHD), in 20 people with coronary heart disease and arterial hypertension, and in 40 healthy people. Statistical analysis was carried out using IBM SPSS Statistics and Microsoft Office Excel 2016 programs with the calculation of non-parametric criteria.

Results: men with minimal hepatitis C virus (HCV) activity predominated among the patients. The majority of patients without accompanying pathologies were young, and those with arterial hypertension and coronary heart disease were elderly. In patients with viral hepatitis C, persons with concomitant cardiovascular pathology (ischemic heart disease and arterial hypertension), the following was observed: a decrease in the content of platelets, erythrocytes; increase in the number of rod neutrophils, ESR, de Ritis coefficient; an increase in the integral index of severity, indices of non-specific immunoreactivity (RC, IRI, IRLM, Ilymph) and endogenous intoxication (HII and II). Also, in these patients, the levels of platelets and lymphocytes were reduced against the background of an increased level of II compared to patients who had viral hepatitis C with only hypertension.

Conclusions: in patients with chronic viral hepatitis C, who have arterial hypertension and coronary heart disease, there is a decrease in the content of platelets, erythrocytes and an increase in rod-shaped

neutrophils, ESR, de Ritis coefficient, integral indicators of severity, indices of non-specific immunoreactivity and endogenous intoxication in comparison with patients without coronary heart disease and patients with chronic HCV only.

Keywords: chronic viral hepatitis C, coronary heart disease, arterial hypertension, liver fibrosis, nonspecific immunoreactivity, endogenous intoxication, health.

Corresponding author: *Kateryna Sumtsova, Department of Infectious Diseases and Epidemiology, Sumy State University, Sumy, Ukraine, e-mail: katya.sumtsova@gmail.com*

РЕЗЮМЕ

Катерина Сумцова
https://orcid.org/0009-0004-8410-8672
Кафедра інфекційних хвороб з епідеміологією, Сумський державний університет, м. Суми, Україна

Владислав Бережок
https://orcid.org/0009-0004-5102-2629
Кафедра інфекційних хвороб з епідеміологією, Сумський державний університет, м. Суми, Україна

Анастісія Лішневська
https://orcid.org/0000-0002-3388-1508
Кафедра інфекційних хвороб з епідеміологією, Сумський державний університет, м. Суми, Україна

Микола Чемич
https://orcid.org/0000-0002-7085-5448
Кафедра інфекційних хвороб з епідеміологією, Сумський державний університет, м. Суми, Україна

ЗАЛЕЖНІСТЬ ЗМІН ЛАБОРАТОРНИХ ПОКАЗНИКІВ У ХВОРИХ НА ВІРУСНИЙ ГЕПАТИТ С ВІД СУПРОВІДОЇ ПАТОЛОГІЇ

Мета: встановити залежність змін гематологічних, біохімічних показників та індексів неспецифічної реактивності, запалення, ендогенної інтоксикації у хворих на хронічний вірусний гепатит С (ХВГС) від супровідної патології.

Матеріали та методи: гематологічні, біохімічні, неспецифічні імунологічні зміни було проаналізовано у 20 хворих на ХВГС без патологій з боку серцево-судинної системи, у 20 пацієнтів з ХВГС з супутньою ішемічною хворобою серця, у 20 осіб з ішемічною хворобою серця та артеріальною гіпертензією та 40 здорових осіб. Статистичний аналіз проводився у програмах IBM SPSS Statistics та Microsoft Office Excel 2016 з розрахунком непараметричних критеріїв.

Результати: серед хворих переважали чоловіки з мінімальною активністю ХВГС. Більшістю пацієнтів без супутніх патологій були молоді особи, а з артеріальною гіпертензією та ішемічною хворобою серця – похилого віку. У хворих на вірусний гепатит С осіб, що мають супутню серцево-судинну патологію (ішемічна хвороба серця та артеріальна гіпертензія) спостерігали: зниження вмісту тромбоцитів, еритроцитів; підвищення кількості паличкоядерних нейтрофілів, ШОЕ, коефіцієнт де Рітіса; збільшення інтегрального показника тяжкості, індексів неспецифічної імунореактивності (КР, ІІР, ІСЛМ, Ілімф) та ендогенної інтоксикації (ГПІ та ПІ). Також у даних хворих були знижені рівні тромбоцитів та лімфоцитів на тлі підвищеного рівня ПІ у порівнянні з пацієнтами, у яких був вірусний гепатит С лише з артеріальною гіпертензією.

Висновки: у хворих на хронічний вірусний гепатит С, які мають артеріальну гіпертензію та ішемічну хворобу серця, спостерігається зниження вмісту в крові тромбоцитів, еритроцитів та збільшення паличкоядерних нейтрофілів, ШОЕ, коефіцієнта де Рітіса, інтегральних показників тяжкості, індексів неспецифічної імунореактивності та ендогенної інтоксикації у порівнянні з хворими без ішемічної хвороби серця та пацієнтів лише з ХВГС.

Ключові слова: хронічний вірусний гепатит С, ішемічна хвороба серця, артеріальна гіпертензія, фіброз печінки, неспецифічна імунореактивність, ендогенна інтоксикація, здоров’я.

Автор, відповідальний за листування: *Катерина Сумцова, кафедра інфекційних хвороб та епідеміології, Сумський державний університет, м. Суми, Україна*
e-mail: katya.sumtsova@gmail.com

Abbreviation: chronic viral hepatitis C – chronic HCV, non-alcoholic steatohepatitis – NASH, acute viral hepatitis C – acute HCV, resistance coefficient – RC, immunoreactivity index – IRI, index of the ratio of neutrophils and monocytes – IRNM, index of the ratio of lymphocytes and monocytes – IRLM, lymphocyte index – Ilymph, index of the ratio of eosinophil and lymphocyte – IREL, allergy index – AI, nuclear index – NI, integral indicator of severity – IIS, entropy of the leukocyte blood formula – ELF, leukocytic index of intoxication – LII, index of aggression – Iagr, hematological index of intoxication – HII, index of leukocyte shift – ILS, index of intoxication – II, reactive response of neutrophils – RRN, total inflammation index – TII, Krebs index – KI, lymphocyte granulocytic index – LGI, index of leukocyte ratio and erythrocyte sedimentation rate – IL ESR, erythrocyte sedimentation rate – ESR, coronary heart disease – CHD

INTRODUCTION / ВСТУП

In the world, about 350 million people suffer from viral hepatitis [1], of which more than 71 million people are infected with the hepatitis C virus (HCV), which is about 20.3% of the total incidence of HCV and about 1.0% of the entire population of the globe [2]. Among those infected with HCV, 58 million people have chronic HCV, and the number of new infections each year reaches about 1.5 million [3].

The incidence of HCV varies in different countries. According to the data of the Public Health Center of Ukraine, the following number of people fell ill with viral hepatitis: in 2022 – 4,002 people (208 – acute HCV, 2,546 – chronic HCV), in 2021 – 4,186 people (203 – acute HCV, 2,707 – chronic HCV) [4].

The dependence of the occurrence of cardiovascular pathology in patients with chronic HCV was found. HCV leads to metabolic disorders, development of chronic inflammation and atherosclerosis [5]. The latter directly affect the development of coronary heart disease, which can lead to acute coronary syndrome and death of the infected person. In patients with cardiovascular pathology, there is a tendency to increase the levels of neutrophils, monocytes, eosinophils and basophils in the blood [6]. A high level of these leukocytes was associated with an increased level of mortality from this pathology. Mutually opposite changes in the quantitative ratio of lymphocytes are an independent risk factor for atherosclerotic disease. That is, the increase and decrease of lymphocytes in peripheral blood correlates with an increased risk of developing atherosclerotic changes in the intima of vessels [7].

At the same time, some studies prove the absence of dependence between CHD and liver pathology. In a Mendelian randomized study, the effect of NASH on arterial stiffness was confirmed, but a causal relationship with coronary heart disease was not found [8]. Although most studies have focused on the relationship between NASH and CHD, the dependence of the course of CHD in liver cirrhosis, especially in the late stage of decompensation, should also be taken into account. A tendency towards an asymptomatic course of CHD in liver cirrhosis was established. This does not claim a complete absence of symptoms, only that the clinical picture of CHD has an atypical course. Therefore, some researchers still emphasize that more attention is needed to the cardiovascular system in case of liver pathology and vice versa [9].

The results of one of the studies prove that a higher prevalence of hypertension was associated with the progression of fibrosis and advanced age. There are several factors that are associated with a significant incidence of hypertension in patients with HCV compared to the general population. The development of inflammation contributes to the development of atherosclerosis and vascular damage: ceramides contribute to the development of an inflammatory state in patients suffering from HCV. The consequence of the inflammatory state is apoptosis of adipocytes, mobilization of macrophages, inflammatory infiltration and release of oxygen free radicals, α-tumor necrosis factor, free fatty acids, which contribute to the development of liver steatosis, insulin resistance, obesity and, as a result, the development of atherosclerosis and hypertension. Extrahepatic signs of HCV, such as membranous and membranoproliferative glomerulonephritis, can also be a cause of hypertension. Along with the progression of liver fibrosis, an increase in the frequency of hypertension in the main group of patients with HCV has been proven [10].

With decompensated cirrhosis, especially with a long course, there is a predominance of vasodilatation over vasoconstriction, as well as a decrease in blood pressure. Portal hypertension and ascites in patients with liver cirrhosis leads to significant hemodynamic changes, which contribute to a decrease in blood pressure due to the development of alternative portosystemic connections [10].

Objective: to establish the dependence of changes in hematological, biochemical indicators and indexes of nonspecific reactivity, inflammation, endogenous intoxication in patients with chronic HCV on accompanying pathology.

Materials and methods

A total of 80 people were examined, of which 60 were patients with chronic HCV and 20 were healthy. The patients were treated at the Z. Krasovytsky Medical Clinical Center of Infectious Diseases and Dermatology. The comparison group underwent a routine medical examination at the University Clinic of Sumy State University.

The examined are divided, depending on the presence or absence of concomitant pathology, into 4 groups, 20 people in each: group A – practically healthy people (comparison group); group B – patients with chronic HCV and arterial hypertension; group C – persons with chronic HCV, arterial hypertension and CHD; group D – patients with chronic HCV (without concomitant cardiovascular pathology).

When participating in the examination, patients were excluded from autoimmune diseases: cryoglobinuria, psoriasis, thyroid disease, other autoimmune diseases of the thyroid gland, hyper/hypothyroidism, Recklinghausen's disease, rheumatoid arthritis, rheumatic heart disease, glomerulonephritis.

The subjects underwent clinical (Elite 3, CobasMicros) and biochemical blood tests (ChemWell, COBASEMira). And also: indicators of non-specific reactivity (RC, IRI, IRNM, IRLM, Ilymph, AI, NI); general integrative indicators (IIS); indices of endogenous intoxication (LII, Iagr, HII, ILS, II, RRN); indices of inflammatory activity (TII, KI, LGI, IL ESR) [11–13].

With the help of Microsoft Office Excel 2016 spreadsheets, input information was collected and its correction and systematization was carried out. Statistical analysis of non-parametric indicators was performed using IBM SPSS Statistics v.23 (IBM Corporation).

According to the constructed Gaussian curve and the Shapiro–Wilk test ($p < 0.05$), the distribution in the groups did not correspond to normal, therefore, non-parametric analysis methods were used for calculation. For this, the Mann–Whitney U-test was used. Criteria were considered reliably significant at $p < 0.05$. Median (Me), 25th and 75th quartiles were used to describe quantitative measures.

The research was carried out in compliance with the norms of international and national legislation on ethics.

Results

In the studied groups, there were 2.0 times more men (67%) than women (33%). The distribution of groups by gender was as follows: A – 55% men and 45% women; B – 70% and 30%; C – 65% and 35%; D – 80% and 20%, respectively, of men and women. In the studied patients, with age, there is a tendency to the occurrence of arterial hypertension and the progression of the pathology to the development of other complications of the cardiovascular system, in particular CHD.

Most of the young people were in groups B and D. Among patients with chronic HCV, arterial hypertension, and coronary heart disease, elderly people predominated, which were 13 times less in group B, and were absent in the group with chronic HCV without concomitant cardiovascular pathology. People of mature age were in all groups, while long-lived people were observed only in group C (Fig. 1).

Minimal activity of liver damage prevailed in patients, moderate activity was 1.4 times less, pronounced activity was observed only in group B (Fig. 2).

With the addition of concomitant pathology, the degree of liver fibrosis (determined by METAVIR) increased (Fig. 3).

In patients of group B, F3 fibrosis was absent, F4 fibrosis prevailed, which was 1.4 times more than with F2 and F0, and 2.3 times more than with F1.

Half of the patients in group C were from F4, which is 2 times more than F2, 2.5 times more than F1, and 10 times more than F0.

In patients of group D, fibrosis F0 prevailed, which is 1.5 times more than in F1 and F2, and in 3.5 times than in F3 and in 2.3 times than in F4.

With the addition of concomitant pathology, an increase in patients with F4 fibrosis was established. That is, there is a dependence of the progression of liver fibrosis and associated diseases compared to individuals of group D.

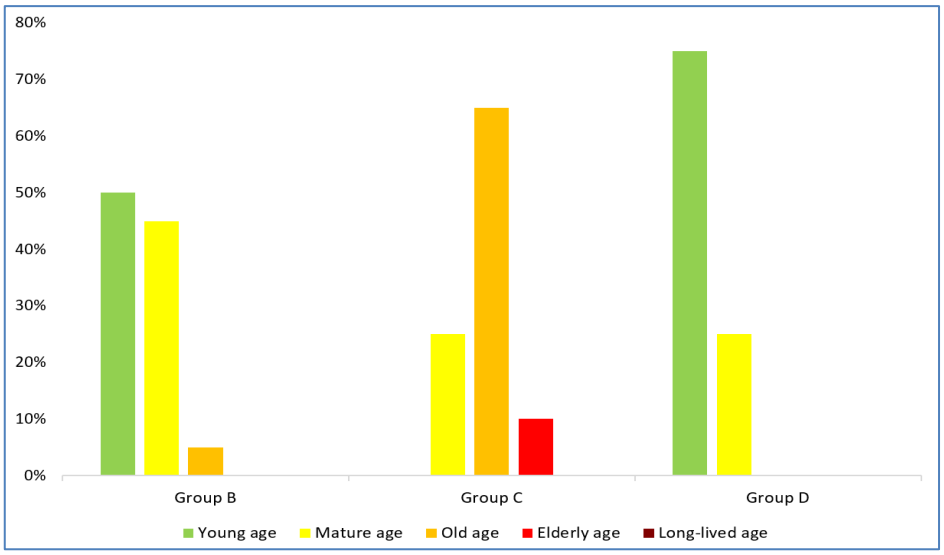

Figure 1 – Distribution of chronic HCV patients by age

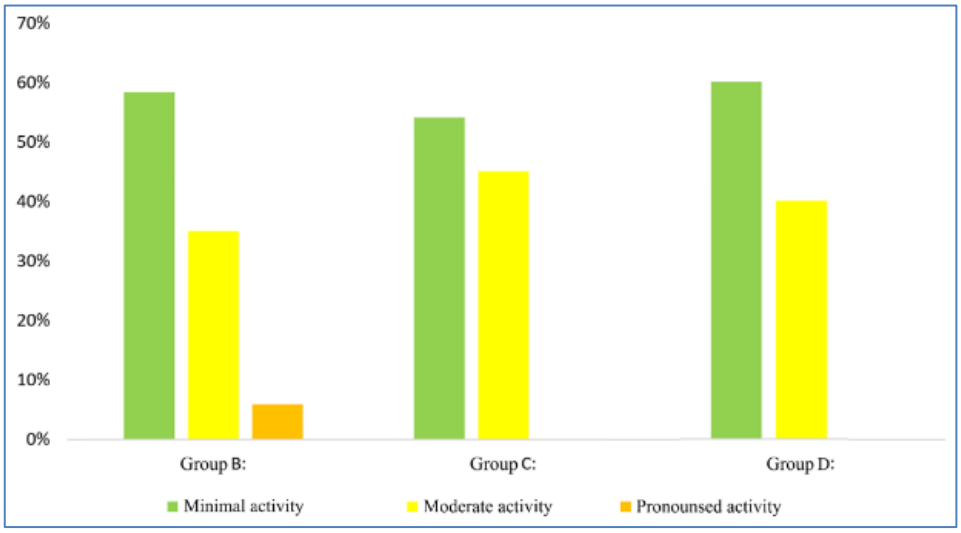

Figure 2 – Distribution of chronic HCV patients by degree of activity

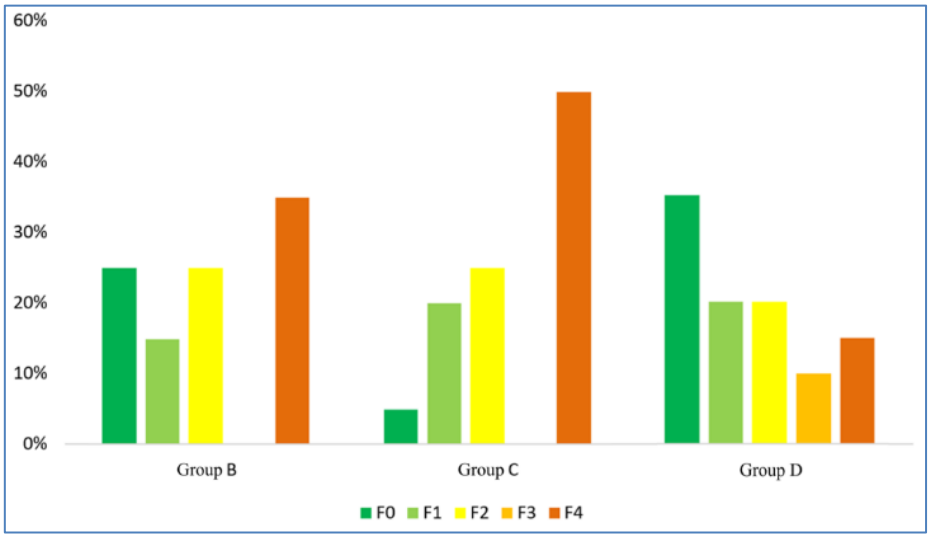

Figure 3 – Distribution of chronic HCV patients by degree of fibrosis

APRI values increased both in patients with chronic viral hepatitis C and hypertension, and in individuals with chronic HCV combined with hypertension and coronary heart disease, compared to individuals with viral hepatitis alone.

Among the hematological indicators, a significant difference was found in the number of platelets: the platelet content in patients from group C was 1.6 times lower than in A and 1.4 times lower than in B ($p < 0.05$). In those examined from group C, the number of platelets was 1.5 times higher than in A ($p < 0.05$) (Table 1).

Table 1 – Changes in hematological indicators in patients with chronic HCV depending on accompanying pathology

Indicator	Group, n				p
	A	B	C	D	
Leukocytes (1×10^9 /l)	5,50 (4,45; 5,50; 7,00)	5,57 (4,33; 5,57; 6,82)	5,57 (3,54; 5,57; 5,96)	6,51 (5,43; 6,51; 7,58)	p_1=0,137; p_2=0,379; p_3=0,871; p_4=0,026*; p_5=0,079; p_6=0,552
Erythrocytes (1×10^{12}/l)	4,64 (4,26; 4,64; 4,92)	4,87 (4,31; 4,87; 5,15)	4,44 (4,17; 4,44; 4,88)	4,66 (4,40; 4,66; 5,04)	p_1=0,552; p_2=0,365; p_3=0,285; p_4=0,120; p_5=0,626; p_6=0,107
Hemoglobin (g/l)	135,50 (130,25; 135,50; 139,50)	145,00 (128,00; 145,50; 158,00)	133,00 (120,75; 133,00; 150,25)	148,00 (139,75; 148,00; 155,00)	p_1=0,004*; p_2=0,655; p_3=0,189; p_4=0,013*; p_5=0,636; p_6=0,119
Platelets (1×10^9/l)	227,50 (197,50; 227,50; 262,25)	204,00 (152,75; 204,00; 228,75)	141,00 (115,00; 141,00; 193,00)	190,00 (164,50; 190,00; 248,25)	p_1=0,168; p_2=0,001*; p_3=0,055; p_4=0,021*; p_5=0,665; p_6=0,037*
Rod nuclear neutrophils (%)	4,00 (2,00; 4,00; 5,00)	3,50 (2,25; 3,50; 6,00)	5,00 (3,00; 5,00; 7,75)	2,5 (2,00; 2,50; 4,00)	p_1=0,071; p_2=0,163; p_3=0,763; p_4=0,007*; p_5=0,055; p_6=0,294
Segmented neutrophils (%)	55,00 (50,25; 55,00; 58,75)	44,50 (40,25; 44,50; 49,50)	49,50 (44,50; 49,50; 54,75)	50,00 (40,25; 50,00; 57,25)	p_1=0,104; p_2=0,058; p_3=0,000*; p_4=0,978; p_5=0,151; p_6=0,056
Eosinophils (%)	2,00 (1,25; 2,00; 4,00)	2,00 (1,00; 2,00; 4,00)	2,00 (1,00; 2,00; 3,00)	3,00 (1,25; 3,00; 4,00)	p_1=0,815; p_2=0,175; p_3=0,440; p_4=0,189; p_5=0,520; p_6=0,709
Lymphocytes (%)	31,00 (29,00; 31,00; 34,75)	38,00 (33,25; 38,00; 40,00)	31,50 (24,50; 31,50; 36,00)	36,50 (29,25; 36,50; 38,75)	p_1=0,039*; p_2=0,828; p_3=0,001*; p_4=0,060; p_5=0,278; p_6=0,005
Monocytes (%)	7,00 (5,25; 7,00; 9,75)	8,00 (7,00; 8,00; 11,75)	10,50 (7,00; 10,50; 11,75)	7,75 (6,00; 7,75; 10,00)	p_1=0,541; p_2=0,064; p_3=0,184; p_4=0,216; p_5=0,505; p_6=0,642

*Notes: * – significant difference according to the Mann–Whitney test ($p < 0.05$); p_1 (group A/group D), p_2 (group A/group C), p_3 (group A/group B), p_4 (group D/group C), p_5 (group D/group B), p_6 (group C/group B)*

The erythrocyte sedimentation rate was the highest in group C (15.00 (5.25–23.75)), which is 2.7 times more than in patients of group D (5.50 (4.00–9.50)) ($p < 0.05$).

A lower level of hemoglobin was found in patients with chronic HCV, arterial hypertension and coronary heart disease compared to patients without concomitant cardiovascular pathology ($p < 0.05$)

The number of rod-shaped neutrophils was 2 times higher in patients with chronic HCV and coronary heart disease compared to patients without complications from the cardiovascular system ($p < 0.05$). Segmented neutrophils were 1.2 times higher

in the control group than in subjects with chronic HCV and arterial hypertension ($p < 0.05$).

The number of lymphocytes was 1.2 times higher in chronic HCV patients without concomitant cardiovascular pathology and in patients with arterial hypertension compared to controls; while the values of lymphocytes were higher in subjects with existing arterial hypertension than in group C ($p < 0.05$).

When analyzing the activity of aminotransferases, their increase is observed, in particular, in ALT indicators there is a tendency to decrease activity with the addition of arterial hypertension (B – 62.00 (54.25–162.00); D – 71.55 (42.75–138, 25)) with a further complication in the form of CHD (C – 48.00 (34.00–141.25)) compared to practically healthy ones (A – 22.50 (17.32–26.87)).

Compared to practically healthy individuals, patients with viral hepatitis have significantly higher AST values (A – 25.28 (19.00–29.10); B – 56.50 (35.75–75.25); C 55.50 (33.50–123.57); D – 52.00 (33.45–72.35)), $p < 0.05$.

The reliability of GGT indicators is also high, but there is no certain dependence of GGT changes in the studied groups in the presence or absence of concomitant disease (A – 29.90 (19.82–46.75); B – 49.00 (31.50–86, 50); C – 63.00 (25.00–101.50); D – 70.00 (37.75–112.65)).

Glucose content in patients remained lower compared to the comparison group, but a gradual increase can be seen with the addition of pathologies (A – 5.75 (5.26–51); B – 5.00 (4.80–5.67); C – 5.20 (4.65–5.80); D – 4.85 (4.25–5.68), $p < 0.05$). Similar changes were observed with creatinine indicators (A – 95.10 (68.50–108.75); B – 76.50 (61.50–81.00); C – 78.52 (69.27–98, 75); D – 76.00 (67.00–91.25), $p < 0.05$).

The de Ritis coefficient was 1.2 times lower in group D compared to practically healthy patients and 1.5 times lower than patients from group C ($p < 0.05$).

According to other indicators: alkaline phosphatase, total protein, bilirubin, no significant changes were detected ($p > 0.05$).

The integral index of severity had the highest values in patients with chronic HCV and two concomitant cardiovascular diagnoses ($p < 0.05$) (Table 2).

Among patients with chronic HCV with concomitant cardiovascular pathology, significantly higher rates of non-specific reactivity were found in patients from group B compared to group C (ELF, RC, IRI, IRLM, Ilymph; $p < 0,05$). In patients of group C, the AI is 2.0 times higher than in patients of group A, and the IRI is 1.4 times lower ($p < 0.05$).

Indices of inflammatory activity changed differently in patients with concomitant diseases: IL ESR was 2.2 times higher in group C compared to group D, KI was 1.4 times higher, and LGI was 1.4 times lower in patients of group C ($p < 0.05$).

Indices of endogenous intoxication had the same tendency in patients with cardiovascular changes: in patients of group C, compared to group D, higher values of HII (1.5 times) and II (3.2) were observed. In addition, II is 3.2 times higher in group C than in group B ($p < 0.05$). Thus, in patients from group C, endogenous intoxication is more pronounced than in group B, and in the latter – than in patients without accompanying pathology.

Analyzing the changes in the IL ESR index (Table 2), we established an increase in its levels (group D) before the appearance of a concomitant disease (group B) and complications (group C) from the cardiovascular system. The indicator of endogenous intoxication had a similar dependence, but the increase occurred with a decrease in indicators relative to group A (Table 2). The entropy of the leukocyte formula (Table 2) had no previous tendency to change, but, like the above data, it was increased compared to group A ($p <0.05$).

Without tendencies to fluctuations, the following indicators were reduced in groups of patients with concomitant diseases: IRI, IRNM, KI, ISL (Table 2).

The lymphocyte-granulocyte index was higher in groups D by 1.3 times and in groups B by 1.4 times, relative to group A (Table 2).

The RC indicator is increased compared to the norm in all groups. Such an indicator as IA slightly deviates from the values in a relatively healthy group (Table 2).

Discussion

During the analysis of the conducted scientific studies, the dependence of the occurrence of cardiovascular pathology in patients with chronic HCV was revealed. HCV leads to metabolic disorders, the development of chronic inflammation and atherosclerosis [5], which plays an almost key role in the development of cardiovascular pathology in individuals with chronic HCV. In this study, this is confirmed by an increase in the number of rod-shaped neutrophils, ESR, de Ritis coefficient, RC, IRI, IRLM, Ilymph, HII and II in subjects with chronic HCV who have concomitant cardiovascular pathology, compared to individuals without it.

Table 2 – Integrative indicators of non-specific immunoreactivity, inflammation and endogenous intoxication in patients with chronic HCV

Indicator	Groups				p
	A	B	C	D	
General integrative indicators					
IIS	14,07 (13,69; 14,07; 14,70)	14,05 (13,75; 14,05; 14,75)	14,92 (13,82; 14,92; 16,05)	13,90 (13,60; 13,90; 14,40)	p_1=0,482; p_2=0,646; p_3=0,028**; p_4=0,011; p_5=0,229; p_6=0,070
ELF	20,78 (18,59; 20,78; 22,57)	23,04 (20,21; 23,04; 26,46)	28,64 (22,82; 28,64; 32,78)	28,25 (20,37; 28,35; 33,39)	p_1=0,005; p_2=0,055; p_3=0,000**; p_4=0,829; p_5=0,060; p_6=0,021**
Indicators of non-specific reactivity					
RC	0,57 (0,50; 0,57; 0,66)	0,88 (0,67; 0,88; 0,99)	0,63 (0,48; 0,63; 0,77)	0,76 (0,52; 0,76; 0,95)	p_1=0,053; p_2=0,000**; p_3=0,394; p_4=0,344; p_5=0,239; p_6=0,025**
IRI	4,85 (3,42; 4,85; 6,30)	4,68 (3,39; 4,68; 6,57)	3,50 (2,16; 3,50; 4,50)	4,78 (3,44; 4,78; 7,48)	p_1=0,860; p_2=0,978; p_3=0,045**; p_4=0,042,; p_5=0,860; p_6=0,050
IRNM	8,08 (5,95; 8,08; 11,09)	6,18 (4,28; 6,18; 7,13)	5,27 (4,45; 5,27; 8,36)	6,81 (4,41; 6,81; 9,49)	p_1=0,176; p_2=0,012**; p_3=0,027**; p_4=0,358; p_5=0,291; p_6=0,978
IRLM	4,50 (3,04; 4,50; 5,97)	4,55 (3,08; 4,55; 6,37)	3,27 (2,08; 3,27; 4,41)	4,50 (3,13; 4,50; 7,48)	p_1=0,745; p_2=0,989; p_3=0,051**; p_4=0,062; p_5=0,808; p_6=0,033**
Ilymph	0,53 (0,47; 0,53; 0,59)	0,77 (0,60; 0,77; 0,86)	0,56 (0,42; 0,56; 0,74)	0,70 (0,49; 0,70;0,90)	p_1=0,040**; p_2=0,000; p_3=0,499; p_4=0,213; p_5=0,409; p_6=0,028**
IREL	0,08 (0,03; 0,08; 0,12)	0,05 (0,02; 0,05; 0,10)	0,05 (0,02; 0,05; 0,11)	0,10 (0,04; 0,10; 0,11)	p_1=0,882; p_2=0,130; p_3=0,433; p_4=0,786; p_5=0,408; p_6=0,579
AI	1,00 (0,79; 1,00; 1,19)	1,18 (1,02; 1,18; 1,48)	0,91 (0,64; 0,91; 1,43)	1,05 (0,88; 1,05; 1,54)	p_1=0,379; p_2=0,045**; p_3=0,525; p_4=0,168; p_5=0,417; p_6=0,079
NI	0,07 (0,03; 0,07; 0,10)	0,08 (0,05; 0,08; 0,13)	0,10 (0,6; 0,10; 0,18)	0,05 (0,03; 0,05; 0,07)	p_1=0,0137**; p_2=0,239; p_3=0,086; p_4=0,010**; p_5=0,024; p_6=0,379
Indices of inflammatory activity					
TII	6,99 (5,85; 6,99; 7,77)	6,87 (6,53; 6,87; 7,49)	7,24 (6,20; 7,24; 8,40)	6,78 (6,11; 6,78; 7,16)	p_1=0,626; p_2=0,871; p_3=0,372; p_4=0,245; p_5=0,351; p_6=0,516
KI	1,85 (1,68; 1,85; 2,10)	1,29 (1,15; 1,29; 1,65)	1,75 (1,34; 1,75; 2,35)	1,43 (1,11; 1,43; 2,05)	p_1=0,040**; p_2=0,000**; p_3=0,499; p_4=0,213; p_5=0,409; p_6=0,028**
LGI	5,12 (4,55; 5,12; 5,75)	7,32 (5,78; 7,32; 8,32)	5,40 (4,17; 5,40; 7,05)	6,61 (4,67; 6,61; 8,54)	p1=0,055; p2=0,001**; p3=0,561; p4=0,234; p5=0,387; p6=0,019**
IL ESR	0,36 (0,18; 0,36; 0,69)	2,25 (1,62; 2,25; 4,70)	3,87 (1,80; 3,87; 6,79)	1,76 (1,41; 1,76; 2,92)	p_1=0,000**; p_2=0,000**; p_3=0,000** p_4=0,033**; p_5=0,256; p_6=0,185
Indices of endogenous intoxication					
LII	0,44 (0,34; 0,44; 0,75)	0,37 (0,24; 0,37; 063)	0,54 (0,31; 0,54; 1,05)	0,42 (0,21; 0,42; 0,61)	p_1=0,304; p_2=0,245; p_3=0,507; p_4=0,160; p_5=0,925; p_6=0,189
Iagr	0,62 (0,48; 0,62; 1,16)	0,48 (0,34; 0,48; 0,88)	0,72 (0,35; 0,72; 1,64)	0,59 (0,26; 0,59; 0,77)	p_1=0,279; p_2=0,224; p_3=0,570; p_4=0,168; p_5=0,797; p_6=0,291
HII	0,40 (0,29; 0,40; 0,66)	0,39 (0,26; 0,39; 0,66)	0,60 (0,38; 0,60; 1,62)	0,39 (0,20; 0,39; 0,65)	p_1=0,685; p_2=0,850; p_3=0,088; p_4=0,040**; p_5=0,839; p_6=0,486
ILS	1,59 (1,43; 1,59; 1,75)	1,10 (093; 1,10; 1,38)	1,53 (1,04; 1,53; 1,77)	1,27 (0,93; 1,27; 1,74)	p_1=0,054; p_2=0,000**; p_3=0,363; p_4=0,364; p_5=0,317; p_6=0,051
II	0,14 (0,07; 0,14; 0,43)	0,17 (0,06; 0,17; 0,29)	0,35 (0,11; 0,35; 0,87)	0,11 (0,07; 0,11; 0,32)	p_1=0,725; p_2=0,665; p_3=0,079; p_4=0,040**; p_5=0,839; p_6=0,035
RRN	9,60 (7,61; 9,60; 17,36)	8,81 (2,74; 8,81; 18,48)	6,00 (2,07; 6,00; 21,37)	8,86 (0,26; 8,86; 15,76)	p_1=0,213; p_2=0,298; p_3=0,256; p_4=0,674; p_5=0,807; p_6=0,989

*Notes: * – significant difference according to the Mann–Whitney test ($p < 0.05$); p_1 (group A/group D), p_2 (group A/group C), p_3 (group A/group B), p_4 (group D/group C), p_5 (group D/group B), p_6 (group C/group B)*

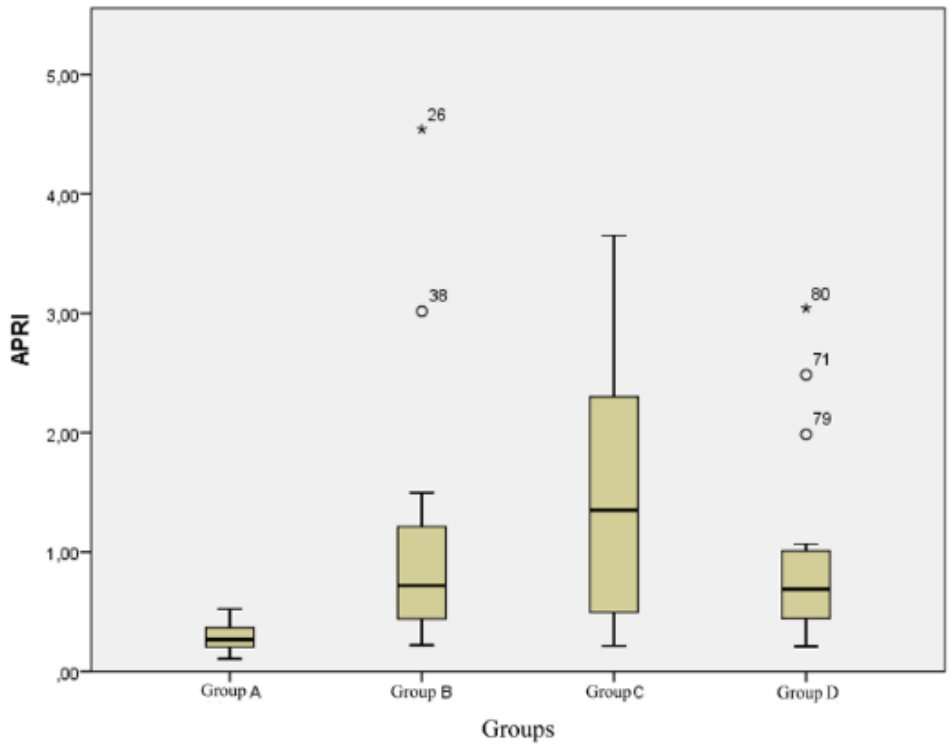

Figure 4 – Distribution of APRI values in patients with chronic HCV

In the conducted study, the vast majority were men, with minimal activity of chronic HCV, which is consistent with the data of previous studies [11, 12].

Aminotransferase levels were associated with an increase in subclinical atherosclerosis, their higher activity was observed in patients with chronic HCV and the presence of subclinical atherosclerosis [15]. In our study, a significant increase in AST and ALT values was observed. ALT indicators showed a tendency to decrease activity with the addition of arterial hypertension with further complication in the form of CHD. This tendency is mainly observed in the older age group, which may be associated with reduced activity of the immune system with age [16] and a longer course of the disease. The most active cytolysis is observed at the beginning of the disease, with the chronicity of the process it decreases, which, in turn, is reflected in a lower level of ALT.

According to the results of our study, an increase in the number of neutrophils in the blood of patients with cardiovascular diseases was observed. This is associated with their participation in the course and formation of atherosclerosis. This theory can be confirmed by a twice-increased number of rod-shaped neutrophils in patients with CHD compared to those examined without concomitant pathologies of the cardiovascular system. The number of segmented neutrophils significantly increased in practically healthy individuals than in hypertensive chronic HCV patients. They participate in the pathogenesis of atherosclerosis due to their extracellular traps, which affect the mechanisms leading to atherogenesis, erosion and destabilization of plaques, by interacting with other populations of immune cells, in particular, mast cells present in the atherosclerotic lesion. This is confirmed by their detection in atherosclerotic plaques [17].

After the analysis of previous studies, a tendency to increase the levels of monocytes, eosinophils and basophils in the general blood test in patients with cardiovascular pathology (not infected with HCV) was established [6]. However, in the above-mentioned results of our studied groups, the indicators of monocytes, eosinophils, erythrocytes turned out to be unreliable ($p > 0.05$). Although there was also a similar trend – with the addition of pathologies from the side of the cardiovascular system, an increase in the number of monocytes was observed, comparable to healthy ones.

The platelet link, namely immature platelets, is associated with mortality and deterioration of the course of acute and stable CHD [18]. Among the indicators of platelets in the studied groups, a decrease in their number was established relative to the comparison group.

Directly proportional changes in the quantitative ratio of lymphocytes are an independent risk factor for atherosclerotic disease. That is, the increase and decrease of lymphocytes in peripheral blood correlates with an increased risk of developing atherosclerotic changes in the intima of vessels [7].

The number of lymphocytes in patients from group D and in patients from group B was 1.2 times higher compared to the comparison group. Higher values of lymphocytes were found in chronic HCV patients without concomitant pathologies. That is, the increase and decrease of lymphocytes in the peripheral blood correlates with the increased risk of developing atherosclerotic changes in the intima of vessels. Under the influence of Th1 cytokines, lymphocytes release tumor necrosis factor α and interferon γ, which have a proatherogenic effect on the arterial wall, their increase in laboratory parameters can precede the development of atherosclerosis and its complications [7].

NASH is a predictor of cardiovascular disease independent of conventional risk factors. Higher mortality in people with NASH compared to the general population has been confirmed. At the same time, cardiovascular diseases are the main cause of death in the population of patients with NASH [19]. There was a trend towards an asymptomatic course of CHD in liver cirrhosis. The results of one of the studies prove that a higher prevalence of hypertension was associated with the progression of fibrosis. Along with the progression of liver fibrosis, an increase in the frequency of hypertension in the main group of patients with HCV has been proven [10]. With the addition of concomitant pathology and its complications (CHD), an increase in the number of patients with liver cirrhosis was established. That is, there is a more intense progression of liver fibrosis in patients with chronic HCV with cardiovascular diseases.

CONCLUSIONS / ВИСНОВКИ

1. The incidence of viral hepatitis C in Ukraine (1.3 million infected) and in the world (over 71 million) remains at a high level.

2. Among the examined, male patients with minimal HCV activity predominate. Most of the young patients had no accompanying pathology, the elderly had hypertension and coronary heart disease.

3. Patients with viral hepatitis C who have concomitant cardiovascular pathology (ischemic heart disease and arterial hypertension) have lower levels of platelets, erythrocytes, but higher levels of rod-shaped neutrophils, ESR and de Ritis coefficient ($p < 0.05$).

4. In patients with viral hepatitis C with arterial hypertension and coronary heart disease, the intergral severity index, most indices of non-specific immunoreactivity (RC, IRI, IRLM, Ilymph), indices of endogenous intoxication (HII and II) were higher ($p < 0.05$).

5. Individuals with chronic HCV, coronary heart disease, and hypertension have the highest APRI scores compared to patients with chronic HCV and hypertension and chronic HCV alone ($p < 0.05$).

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

The work was carried out within the framework of: National Research Institute of the Department of Infectious Diseases and Epidemiology of Sumy State University (SSU) "Clinical-epidemiological features of the course of viral, bacterial and parasitic infections depending on immunological, genetic and metabolic factors, optimization of diagnostic and therapeutic measures" (number of state registration 0121U11571) (implementation period: 2022–2027).

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Chemych M. D. [1,2,3,4]

Lishnevska A. G. [1,2,3,4]

Sumtsova K. O. [1,2,3,4]

Berezhok V. Y. [1,2,3,4]

1. A significant contribution to the design or construction of the manuscript; acquisition, analysis, or interpretation of data for the manuscript.

2. Compilation of the manuscript or critical revision of its important intellectual content.

3. Final approval of the version to be published.

4. Agreed to be responsible for all aspects of the work, ensuring proper investigation and resolution of issues related to the accuracy or integrity of any part of the work.

REFERENCES/СПИСОК ЛІТЕРАТУРИ

1. World Health Organisation. *Hepatitis Summit 2022 statement*. Retrieved from: https://www.who.int/news/item/10-06-2022-world-hepatitis-summit-2022-statement
2. World Health Organisation. *Global hepatitis report, 2017*. Retrieved from: https://www.who.int/publications/i/item/9789241565455
3. World Health Organisation. *Hepatitis C, 2022.* Retrieved from: http://surl.li/sduqj
4. Tsentr hromadskoho zdorovia MOZ Ukrainy. *Statystyka z virusnykh hepatytiv*. [Statistics on viral hepatitis]. Retrieved from: https://www.phc.org.ua/kontrol-zakhvoryuvan/virusni-gepatiti/statistika-z-vg
5. Nevola R, Acierno C, Pafundi PC, Adinolfi LE. Chronic hepatitis C infection induces cardiovascular disease and type 2 diabetes: mechanisms and management. *Minerva Med*. 2021;112(2):188-200. https://doi.org/10.23736/S0026-4806.20.07129-3. PMID: 33205641
6. Pizzolo F, Castagna A, Olivieri O, Girelli D, Friso S, Stefanoni F, Udali S, Munerotto V, Baroni M, Cetera V, Luciani GB, Faggian G, Bernardi F, Martinelli N. Basophil Blood Cell Count Is Associated With Enhanced Factor II Plasma Coagulant Activity and Increased Risk of Mortality in Patients With Stable Coronary Artery Disease: Not Only Neutrophils as Prognostic Marker in Ischemic Heart Disease. *J Am Heart Assoc*. 2021;10(5):e018243. https://doi.org/10.1161/JAHA.120.018243. Epub 2021 Feb 24. PMID: 33624506; PMCID: PMC8174269
7. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. *Signal Transduct Target Ther*. 2022;7(1):131. https://doi.org/10.1038/s41392-022-00955-7. PMID: 35459215; PMCID: PMC9033871
8. Peng H, Wang S, Wang M, Ye Y, Xue E, Chen X, Wang X, Fan M, Gao W, Qin X, Wu Y, Chen D, Li J, Hu Y, Wang L, Wu T. Nonalcoholic fatty liver disease and cardiovascular diseases: A Mendelian randomization study. *Metabolism.* 2022;133:155220. https://doi.org/10.1016/j.metabol.2022.155220. Epub 2022 May 23. PMID: 35618017
9. Gîrleanu I, Trifan A, Huiban L, Muzîca C, Petrea OC, Sîngeap AM, Cojocariu C, Chiriac S, Cuciureanu T, Costache II, Stanciu C. Ischemic Heart Disease and Liver Cirrhosis: Adding Insult to Injury. *Life (Basel).* 2022;12(7):1036. https://doi.org/10.3390/life12071036. PMID: 35888123; PMCID: PMC9315506
10. Rajewski P, Zarębska-Michaluk D, Janczewska E, Gietka A, Mazur W, Tudrujek-Zdunek M, Tomasiewicz K, Belica-Wdowik T, Baka-Ćwierz B, Dybowska D, Halota W, Lorenc B, Sitko M, Garlicki A, Berak H, Horban A, Orłowska I, Simon K, Socha Ł, Wawrzynowicz-Syczewska M, Jaroszewicz J, Deroń Z, Czauż-Andrzejuk A, Citko J, Krygier R, Piekarska A, Laurans Ł, Dobracki W, Białkowska J, Tronina O, Wietlicka-Piszcz M, Pawłowska M, Flisiak R. Hepatitis C Infection as a Risk Factor for Hypertension and Cardiovascular Diseases: An EpiTer Multicenter Study. *J Clin Med.* 2022;11(17):5193. https://doi.org/10.3390/jcm11175193. PMID: 36079122; PMCID: PMC9456581
11. Chemych MD, Lishnevska AG. The role of galectin-9 in patients with chronic viral hepatitis C and its connection with the type of therapy, the degree of fibrosis, clinical, laboratory, autoimmune and integrative indicators. *Wiad Lek.* 2021;74(5):1180-1188.
12. Lishnevska AH, Chemych MD. Changes in clinical, biochemical, immunological and integrative parameters in patients with chronic hepatitis C virus infection according to the virus genotype and the grade of activity. *Zaporozhye Medical Journal*. 2020; 22(4), 485-494. https://doi.org/10.14739/2310-1210.2020.4.208363
13. Lishnevska A, Chemych M, Chemych O, Chernetsky I. Immunoreactivity and intoxication syndrome in patients with chronic viral hepatitis C. *Bangladesh Journal of Medical Science*. 2023; 22 (3): 508 – 514.
14. Iorga RA, Bacalbasa N, Bratu OG, Ionita Radu F, Diaconu CC. The impact of infection with hepatitis C virus on cardiovascular risk. *Am J Cardiovasc Dis*. 2020;10(3):201-206.
15. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between Heart Disease and Liver Disease: A Two-Way Street. *Cells.* 2020;9(3):567. https://doi.org/10.3390/cells9030567. PMID: 32121065; PMCID: PMC7140474
16. Sadighi Akha AA. Aging and the immune system: An overview. *J Immunol Methods.* 2018;463:21-26. https://doi.org/10.1016/j.jim.2018.08.005. PMID: 30114401
17. Döring Y, Libby P, Soehnlein O. Neutrophil Extracellular Traps Participate in Cardiovascular Diseases: Recent Experimental and Clinical Insights. *Circ Res.* 2020;126(9):1228-1241. https://doi.org/10.1161/CIRCRESAHA.120.315931. PMID: 32324499; PMCID: PMC7185047
18. Faber J, Hvas AM, Kristensen SD, Grove EL, Adelborg K. Immature Platelets and Risk of

Cardiovascular Events among Patients with Ischemic Heart Disease: A Systematic Review. *Thromb Haemost.* 2021;121(5):659-675. https://doi.org/10.1055/s-0040-1721386. PMID: 33302302

19. Sao R, Aronow WS. Association of non-alcoholic fatty liver disease with cardiovascular disease and subclinical atherosclerosis. *Arch Med Sci*. 2018;14(6):1233-1244. https://doi.org/10.5114/aoms.2017.68821. Epub 2017 Jul 5. PMID: 30393477; PMCID: PMC6209727

Received 06.12.2023
Accepted 06.02.2024

Одержано 06.12.2023
Затверджено до друку 06.02.2024

INFORMATION ABOUT THE AUTHORS / ВІДОМОСТІ ПРО АВТОРІВ

Kateryna Sumtsova, Rimsky-Korsakov Street, 2; https://orcid.org/0009-0004-8410-8672, phone number +380951678379; katya.sumtsova@gmail.com

Vladyslav Berezhok, Rimsky-Korsakov Street, 2; https://orcid.org/0009-0004-5102-2629, phone number +380971769188; Vlad125115@gmail.com

Anastasiia Lishnevska; Rimsky-Korsakov Street, 2; https://orcid.org/0000-0002-3388-1508, phone number +380997972740; a.lishnevska@kinf.sumdu.edu.ua

Mykola Chemych, Rimsky-Korsakov Street, 2; https://orcid.org/0000-0002-7085-5448, phone number +380506310579; n.chemych@kinf.sumdu.edu.ua