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СОДЕРЖАНИЕ МОЛЕКУЛ МЕЖКЛЕТОЧНОЙ АДГЕЗИИ У ПАЦИЕНТОВ С COVID-19-АССОЦИИРОВАННЫМ ПОРАЖЕНИЕМ ЛЕГКИХ

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The Content of Intercellular Adhesion Molecules in Patients With COVID-19-Associated Lung Disease

Резюме

Цель. Оценить содержание молекул межклеточной адгезии: ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel у пациентов с COVID-19-ассоциированным поражением легких и выявить наличие взаимосвязи между их концентрацией и тяжестью течения процесса. **Материалы и методы.** В исследование были включены 200 пациентов после перенесенного COVID-19-ассоциированного поражения легких через 1 месяц после выписки из моностационаров г. Читы. Исследуемые были разделены на группы по 50 человек, в зависимости от степени поражения легких по результатам проведения компьютерной томографии: 1-я группа (КТ-1), 2-я группа (КТ-2), 3-я группа (КТ-3), 4-я группа (КТ-4). В группу контроля были включены 56 относительно здоровых лиц, не болевших ранее коронавирусной инфекцией и другими острыми респираторными заболеваниями за последние 3 месяца. Все исследуемые группы были сопоставимы по полу и возрасту. Содержание молекул межклеточной адгезии в сыворотки крови определяли методом иммунохимического анализа. **Результаты.** В результате проведенного исследования было выявлено повышенное содержание молекул межклеточной адгезии (ММА) (ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel) у исследуемых групп больных с COVID-19-ассоциированным поражением легких в сравнении с группой контроля. Были обнаружены различия между группами пациентов с разным уровнем поражения легких по данным КТ, при исследовании некоторых молекул межклеточной адгезии. **Заключение.** По итогам проведенной работы выявлено, что после перенесенной коронавирусной инфекции, осложненной поражением легких, в крови наблюдается повышение концентрации молекул межклеточной адгезии — представителей всех исследуемых суперсемейств. Увеличение уровней молекул межклеточной адгезии у исследуемых пациентов отражает наличие эндотелиоза и коррелирует с тяжестью поражения легочной ткани, в том числе и в период реконвалесценции.

Ключевые слова: *COVID-19-ассоциированное поражение легких, молекулы межклеточной адгезии, ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. To evaluate the content of intercellular adhesion molecules: ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel in patients with COVID-19-associated lung damage and to identify the relationship between their concentration and severity the flow of the process. **Materials and methods.** The study included 200 patients after suffering COVID-19-associated lung damage 1 month after discharge from Chita monostationals. The subjects were divided into groups of 50 people, depending on the degree of lung damage according to the results of computed tomography: Group 1 (CT-1), median age was 51.5 [50.5; 54.8]; Group 2 (CT-2), median age 57.0 [53.1; 57.0]; group 3 (CT-3), median age 52.5 [51.9; 55.0]; 4th group (CT-4), median 55.0 [53.2; 56.4]. The control group included 56 relatively healthy individuals who had not previously had coronavirus infection and other acute respiratory diseases in the last 3 months, the median age was 55.0 [51.1; 55.0]. All the study groups were comparable in gender and age. The content of intercellular adhesion molecules in blood serum was determined by immunochemical analysis. **Results.** The study revealed an increased content of intercellular adhesion molecules (MMA) (ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel) in the studied groups of patients with COVID-19-associated lung damage in comparison with the control group. Differences were found between groups of patients with different levels of lung damage according to CT data, when examining some intercellular adhesion molecules. **Conclusion.** According to the results of the work carried out, it was revealed that after a coronavirus infection complicated by lung damage, an increase in the concentration of intercellular adhesion molecules in the blood is observed — representatives of all the studied superfamilies. An increase in the levels of intercellular adhesion molecules in the studied patients reflects the presence of endotheliosis and correlates with the severity of lung tissue damage, including during the period of convalescence.

Key words: *COVID-19-associated lung damage, intercellular adhesion molecules, ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The study was approved by the local Ethics Committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation (extract from Protocol No. 105. December 2, 2020). Informed consent was obtained from all subjects who participated in the study. Written informed consent was also obtained from the patients for the publication of this article.

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IAM — intercellular adhesion molecule, EC — endothelial cells, COVID-19 — novel coronavirus infection

Introduction

Intercellular adhesion molecules (IAM) are cell surface proteins, which participate in binding cells to one another and to the extracellular matrix. They are essential components in maintaining the tissue structure and functions. Also, IAMs participate in cell growth mechanism, contact cell inhibition and apoptosis, endothelial cell (EC) activation at the inflammation site, white blood cell migration from the vascular bed to adjacent tissues, pathogen and toxin eradication, vessel sequestration and remodelling, reparation and hemostasis mechanisms [1]. In the physiologically normal state, endotheliocytes do not express IAMs. Under the influence of damaging factors, IAM concentration on their surface increases, and oxidised lipids and lipoproteins accumulate in larger amounts in the subendothelial area [2]. Excessive, uncontrolled EC activation causes formation of small blood clots, higher vascular permeability, tissue and cell hypoxia, and results in inflammation [1, 3].

In terms of structural similarity, IAMs are stratified into five 5 superfamilies [4]:

1. Integrins (CD29 (β_1), CD18 (β_2), CD61 (β_3), CD49 (β_7), etc.) are hetero-dimeric molecules, which function both as cell substrate and intercellular adhesive receptors.
2. Adhesive receptors from immunoglobulin superfamily (PECAM-1, NCAM, ICAM-1, ICAM-2, ICAM-3, etc.) participate in intercellular adhesion.
3. Selectins (E-, P-, L-selectins) are adhesive receptors, the lectin-like domain of which ensures adhesion of white blood cells to endothelial cells.
4. Cadherins (E-, P-, N-, R-, VE-cadherins) are calcium-dependant adhesion proteins, which ensure contacts between endothelial cells.
5. Homing receptors or addressins (MAdCAM-1, mucosaladressin cellular adhesion molecule-1)), CD34, GlyCAM-1) are molecules, which ensure lymphocyte release to the lymphoid tissue.

Another IAM has been found recently, which is not included in any of the above molecule classes: EPCAM (epithelial cell adhesion molecule, CD326) — a membrane protein, encoded by a same-name gene, which participates in the intercellular adhesion in epithelium, signal transmission to the cell nucleus, cell migration, cell proliferation and differentiation, as well as dissemination of tumours [5].

There are membrane-dependent and soluble IAMs, their main function being regulation of white blood cell migration from the blood flow via endothelium to the cell damage area [2].

The process of white blood cell migration from the vessel bed via endothelium runs in several steps, and IAMs participate in each and every of them. The process of "border standing", as a result of which white blood cells stay at the borderline of the vessel bed, is facilitated by P-selectin. White blood cell activation (early adhesion) is also promoted by selectins (P- and E-selectins). "Other white blood cell adhesion" is ensured by ICAM-1 and ICAM-2 as well as by leucocyte integrins (LFA-1 and Mac 1). Transendothelial white blood cell migration is facilitated by the same integrins and ICAM-1, VCAM-1, PECAM-1 [4].

Given that IAMs participate in immune response and inflammation progression, the academic interest lies in the research of their expression in various contagious pathologies, including COVID-19-assoiciated lung damage.

Study Objective

To study the levels of intercellular adhesion molecules (ICAM-1, ICAM-2, ICAM-3, NCAM, VCAM-1, PECAM-1, E-sel, P-sel, EpCAM, L-sel) in patients with COVID-19-assoiciated lung damage and identify the correlation between their concentration and condition severity.

Materials and Methods

The study included 200 patients, who previously had COVID-19-assoiciated lung damage and were discharged from specialised inpatient clinics in Chita a month before enrolment. All patients were divided into groups of 50 people, depending on the degree of lung damage as seen on CT scans: group 1 (CT1) — median age was 51.5 [50.5; 54.8]; group 2 (CT2) — median age was 57.0 [53.1; 57.0]; group 3 (CT3) — median age was 52.5 [51.9; 55.0]; and group 4 (CT4) — median age was 55.0 [53.2; 56.4]. The study included patients with confirmed COVID-19; they had a positive polymerase chain reaction test for SARS-CoV-2 RNA. Exclusion criteria were: systemic diseases; lymphoproliferative and myeloproliferative disorders requiring immunosuppressive therapy; pregnancy, HIV infection, chronic alcoholism. The control group included 56 healthy volunteers without a history of coronavirus infection and other respiratory diseases within the past three months; median age was 55.0 [51.1; 55.0]. All study groups were comparable in sex and age composition. The levels of serum intercellular adhesion molecules were measured using immunochemical assay. Statistical processing of study results was performed with IBM SPSS Statistics Version 25.0 (licence No. Z125-3301-14, IBM, USA) [6,7].

Results and Discussion

ICAM-1 (CD54) is an integral membrane protein, included in the immunoglobulin superfamily. In the physiologically normal state, its expression by endothelial cells is close to zero. Its expression rises under the influence of free radicals, complement components, nitrogen oxide, lipopolyssacharides, pro-inflammatory cytokines (IL-1, 6, 8; TNF-α, etc.), histamine, leukotriene and other mediators [8–9]. Also, this IAM is expressed by lymphocytes, monocytes, bronchoalveolar epithelial cells, and the expression increases within 6–8 hours after stimulation and persists for 48 hours [2]. The role of ICAM-1 as a marker of diseases, including inflammatory conditions, has been proven by a number of pathological reactions. In allergic inflammation of airways, ICAM-1 promotes the development of nasal allergies. Higher IAM (sICAM-1) levels were found in HIV-1 carriers. According to G.P. Downey and L. Fialkow (1995) [10], plasma sICAM-1 levels are a prediction criterion; a value of over 1,000 ng/mL is a sign of a high probability of death [11]. A study of A/H1N1/09 pneumonias showed that sICAM-1 levels in patients with various degrees of disease severity had multidirectional fluctuations: they were higher in more severe cases and lower in mild pneumonias; in a vast majority of patients with the highest sICAM-1 levels, pneumonia was associated with acute lung damage [12].

An analysis of ICAM-1 concentrations in the study groups showed its higher levels in patients with COVID-19-associated lung damage vs. controls. Group 1 (CT-1) — 1.2 times higher [1.4; 2.03] ($p < 0.001$), group 2 (CT-2) — 1.8 times higher [2.2; 2.2] ($p < 0.001$), group 3 (CT-3) — 1.9 times higher [1.1; 2.2] ($p < 0.001$), group 4 (CT-4) — 2.01 times higher [1.3; 2.8] ($p < 0.001$) (Table 1). Also, lower ICAM-1 concentrations were observed in patients with mild COVID-19-associated lung damage (CT-1) vs. groups CT-2, CT-3, CT-4: 1.4, 1.5 and 1.6 times higher, respectively ($p < 0.001$) (Figure 1).

ICAM-2, another representative of the immunoglobulin superfamily, is found on the cell membrane surface, mostly of hemopoietic cells [2, 13]. Its expression on dormant lymphocytes is higher than that of ICAM-1, whereas the synthesis of these molecules on monocytes is approximately the same. Similarly to ICAM-1, its receptor is integrin LFA-1. Since unlike ICAM-1, ICAM-2 is found on dormant ECs, it is likely to participate in recirculation of LFA-1-positive lymphocytes. Also, ICAM-2 is essential for initiation of T-cell adhesion to antigen-presenting cells. For now, it is assumed that an additional function of ICAM-2 is ICAM-1-independent lysis of various target cells [2, 14].

In this study, ICAM-2 levels were higher in patients in CT-1, CT-3, and CT-4 groups vs. healthy subjects (Table 1): CT-1 — 1.2 times [1.01; 1.3] ($p = 0.025$),

CT-3 — 1.4 times [1.2; 1.7] ($p < 0.001$), CT-4 — 1.6 times [3.5; 1.04] ($p < 0.001$). There are also differences in the concentration of this IAM between the group of mild lung damage (CT-1, CT-2) and the group of severe COVID-19-associated lung damage (CT-3, CT-4) (Figure 2).

ICAM-3 is an integral membrane protein with high homology to ICAM-1 and ICAM-2 in the extracellular region; it is expressed on dormant lymphocytes, monocytes and neutrophils. ICAM-1, ICAM-2, and ICAM-3 are a ligand for LFA-1, which impacts its activity. Unlike ICAM-1 and ICAM-2, ICAM-3 is not present on

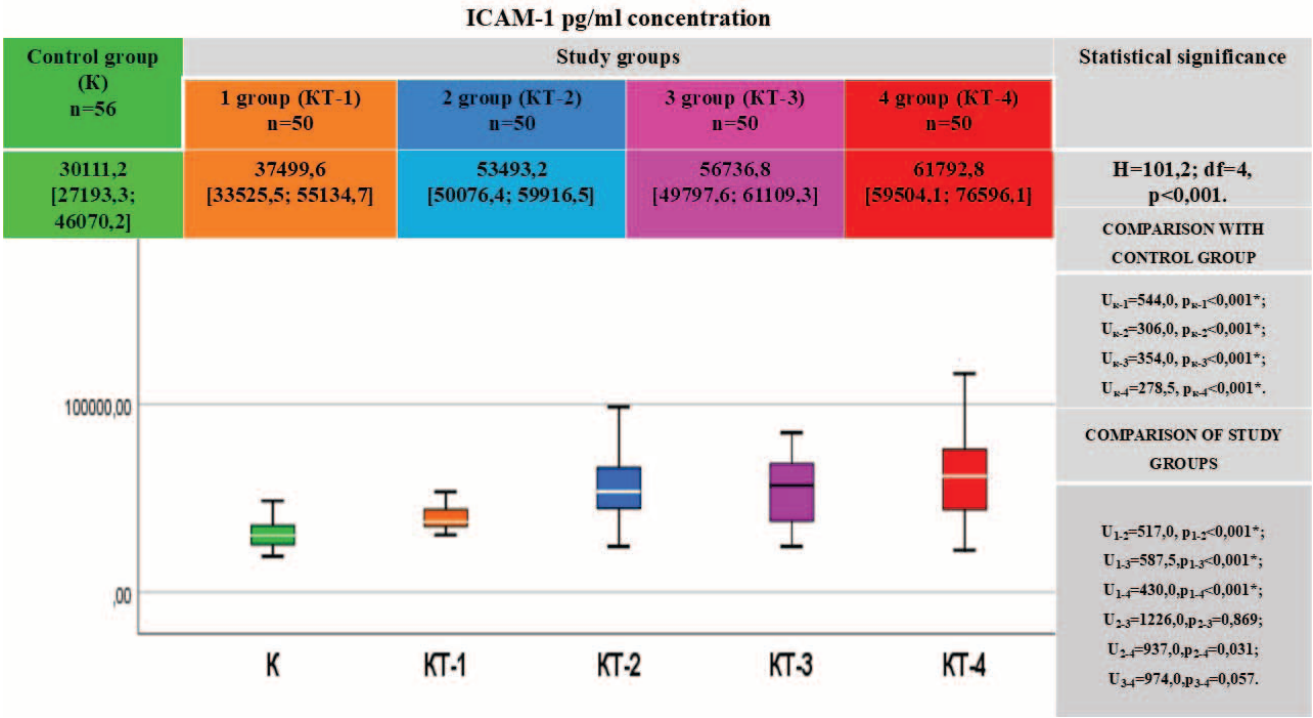

Figure 1. *The concentration of ICAM-1 intercellular adhesion molecules in the blood of patients in the studied groups*

Note: statistical significance of differences between: p_{c-1} — control group and group 1; p_{c-2} — control group and group 2; p_{c-3} — control group and group 3; p_{c-4} — control group and group 4; p_{1-2} — between groups 1 and 2 of patients; p_{1-3} — between 1 and 3 groups of patients; p_{1-4} — between 1 and 4 groups of patients; p_{2-3}– between 2 and 3 groups of patients; p_{2-4} — between 2 and 4 groups of patients; p_{3-4} — between 3 and 4 groups of patients.

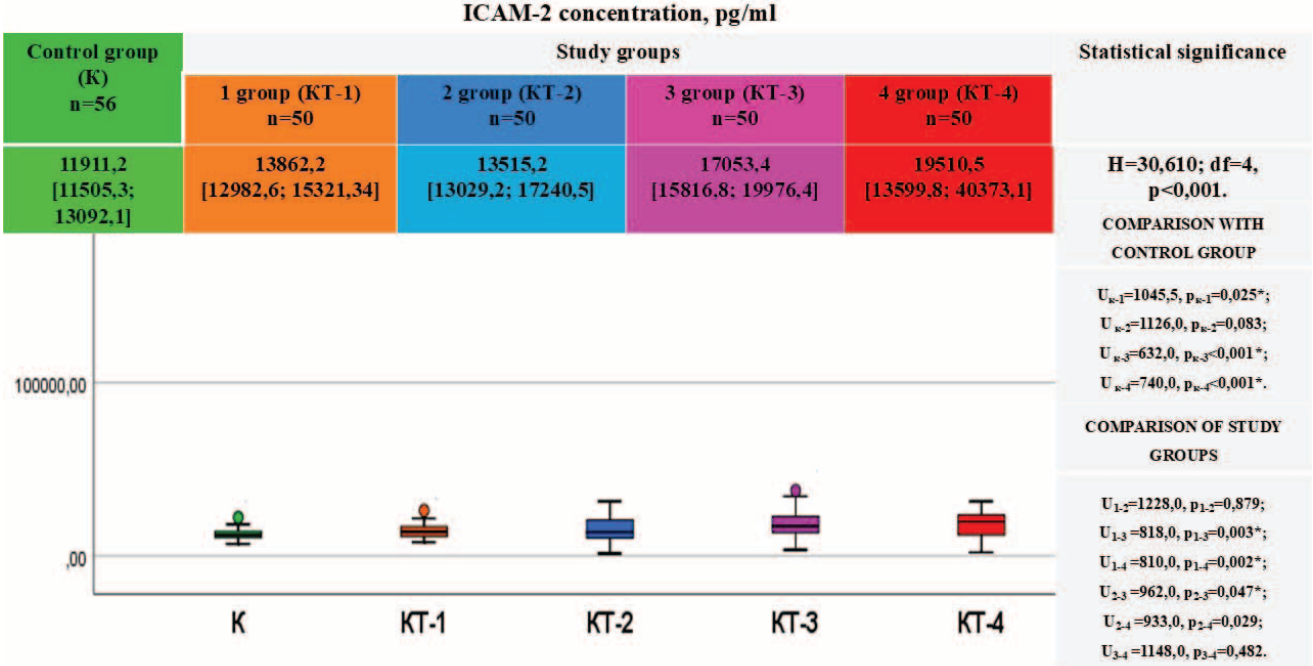

Figure 2. *The concentration of ICAM-2 intercellular adhesion molecules in the blood of patients in the studied groups*

Note: see figure 1

endothelium, but its expression is better on monocytes and dormant lymphocytes vs. other LFA-1 ligands [2, 16]. An analysis of the available information shows that ICAM-3 has a crucial role to play in immune response initiation. It has also been found that this IAM participates in regulation of LFA-1/ICAM-1-dependent intercellular white blood cell interaction. sICAM-3 levels increase in rheumatoid arthritis, systemic lupus erythematosus [1].

An analysis of serum ICAM-3 levels in patients demonstrated higher concentrations in patients with coronavirus infection vs. controls: group 1 (CT-1) — 1.9 times [1.6; 2.7] ($p < 0.001$), group 2 (CT-2) — 1.7 times [1.3; 2.3] ($p < 0.001$), group 3 (CT-3) — 1.4 times [1.1; 2.03] ($p < 0.001$), in group 4 (CT-4) — 1.4 times [1.1; 2.01] ($p < 0.001$). Comparison of patients with COVID-19-associated lung damage revealed statistically significant differences in ICAM-3 concentrations between patients with mild lung damage (CT-1) and patients with severe condition (CT-3, CT-4) ($p = 0.001$). Of note, a higher concentration of this IAM was observed in patients with smaller areas of pulmonary tissue damage caused by coronavirus infection (CT-1) as compared to patients in CT-3 and CT-4 groups: comparison of group 1 (CT-1) and group 3 (CT-3) — 1.4 times [1.03; 1.8] ($p = 0.001$); of group 1 (CT-1) and group 4 (CT-4) — 1.4 times [1.04; 1.8] ($p = 0.001$) (Figure 3).

NCAM (CD56), a neural cell adhesion molecule, is a homophilic binding glucoprotein, which is expressed on the surface of neurons, glia and skeletal muscles. Its expression was also found in the hematopoietic system; it is associated with natural killer cells, but is not limited to them. CD56 was found on other lymphocytes, including γδ T cells and activated CD8+ T cells, as well as dendritic cells. According to present knowledge, NCAM participates in cell adhesion, axon spread, synaptic plasticity, learning, and memory [2,17].

An analysis of this IAM in our patients showed its higher concentrations: group 1 (CT-1) vs. controls — 1.4 times [1.2; 1.6] ($p < 0.001$); group 2 (CT-2) — 1.6 times [1.9; 1.4] ($p < 0.001$); group 3 (CT-3) — 1.8 times [1.5; 2.01] ($p < 0.001$); group 4 (CT-4) — 2.2 times [1.9; 2.5] ($p < 0.001$). There is also difference in NCAM levels between patients with mild COVID-19-associated lung damage (CT-1) and other study groups (CT-2, CT-3, CT-4): 1.1 [1.1; 1.4]; 1.3 [1.1; 1.4]; 1.5 [1.4; 1.7] timely, respectively ($p < 0.001$) (Figure 4).

VCAM-1 is involved in leukocytic-endothelial interaction and expressed after cell stimulation by IL-1, TNF-α or an endotoxin. This IAM is a ligand to integrin VLA-4, found on lymphocytes, monocytes and eosinophils [2]. It participates in white cell adhesion outside vessels, thus ensuring interaction between lymphoblasts and stromal cells of the bone marrow and between B cells and dendritic cells in lymph node follicles. According to the literature, VCAM-1 possesses selective leukocytic adhesion, thus ensuring mononuclear cell accumulation during acute inflammation [18, 19]. Higher VCAM-1 levels were observed in various autoimmune conditions (multiple sclerosis, systemic sclerosis, systemic lupus erythematosus), infections (sepsis, meningitis, malaria) and other [1, 2, 18].

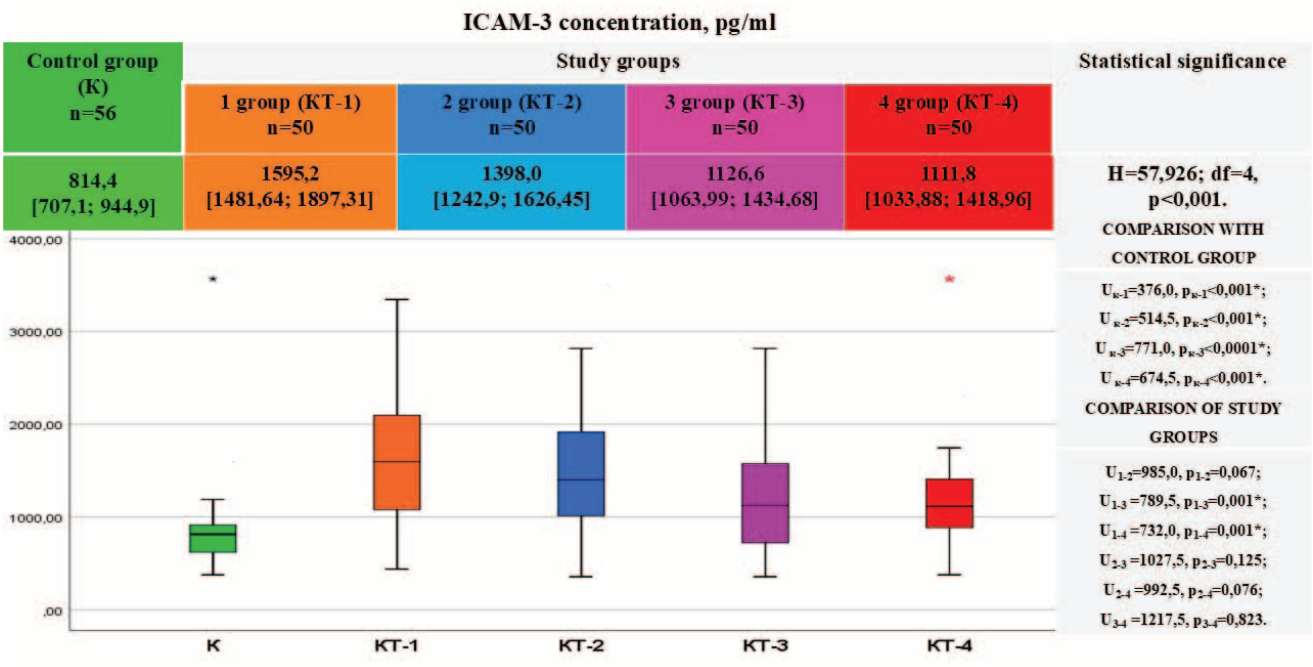

Figure 3. *The concentration of ICAM-3 intercellular adhesion molecules in the blood of patients in the studied groups*
Note: see figure 1

A study of concentrations of this molecule in post-coronavirus infection patients demonstrated higher levels in patients with COVID-19-associated lung damage (CT-2, CT-3, CT-4) vs. controls: 1.3, 1.7, 1.8 times, respectively ($p < 0.001$). Serum VCAM-1 levels were higher in patients with a more severe condition (Figure 5).

PECAM-1 (CD31) is a transmembrane glucoprotein; it is expressed mostly by vascular cells and is an immunohistochemical marker of blood vessel angiogenesis. CD31 was found on platelets, monocytes, neutrophils, and CD8+ T cells [2]. Previous studies confirm PECAM-1 involvement in inflammatory processes and interaction between white blood cells and ECs. It has also been established that, during white cell migration, they enter the inflammation site via intercellular junctions of vessel endotheliocytes under the influence of PECAM-1 [20, 21].

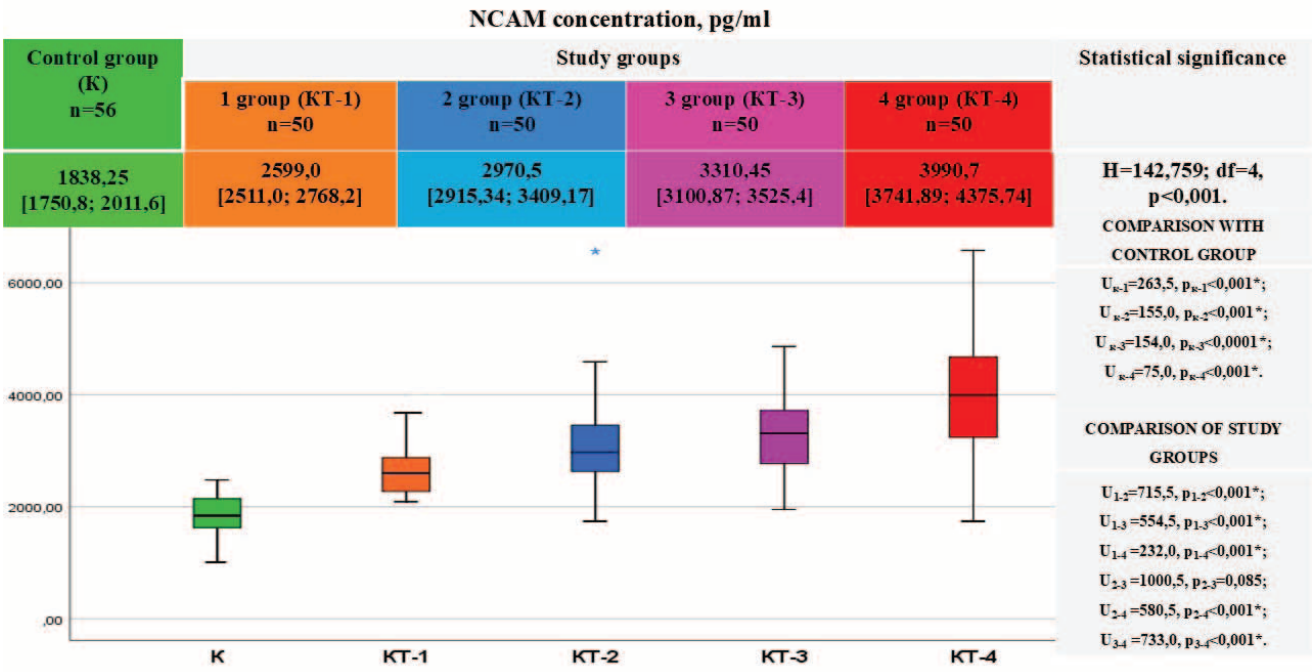

Figure 4. *The concentration of NCAM intercellular adhesion molecules in the blood of patients in the studied groups*
Note: see figure 1

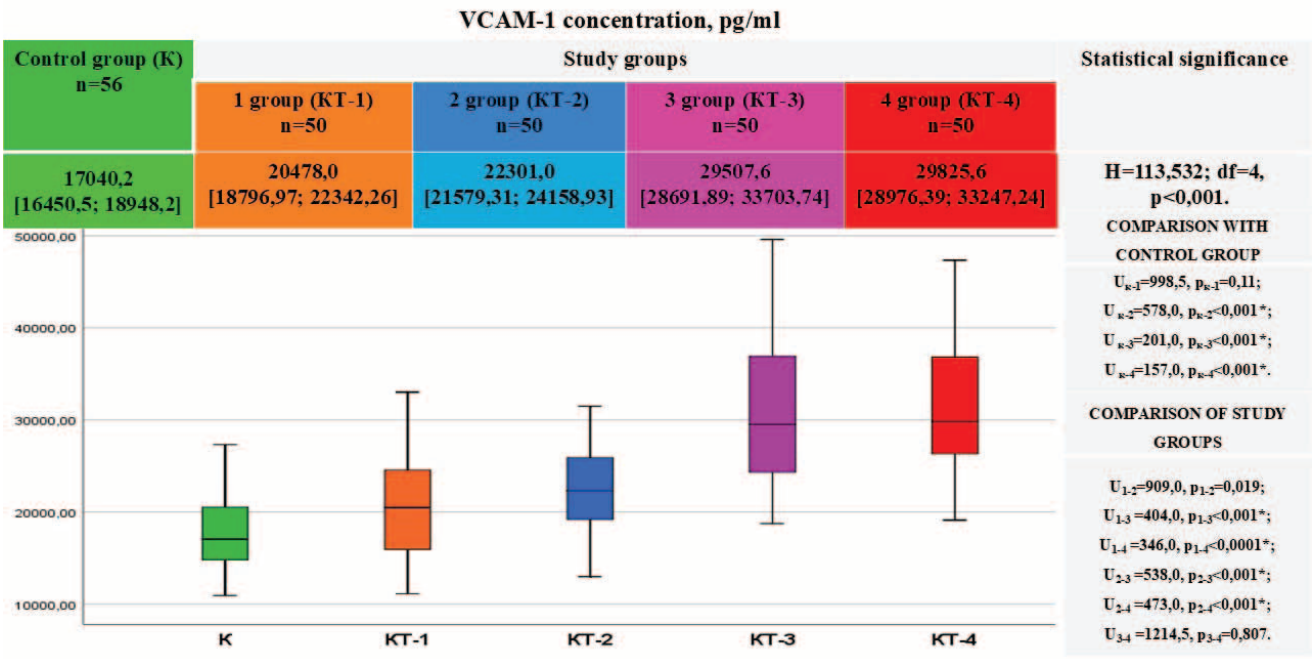

Figure 5. *The concentration of VCAM-1 intercellular adhesion molecules in the blood of patients in the studied groups*
Note: see figure 1

Studies of PECAM-1 showed its higher concentrations in patients vs. controls. Higher PECAM-1 levels were observed in patients with COVID-19-associated lung damage (CT-1) vs. controls: 1.4 times [1.2; 1.6] ($p < 0.001$), and 1.6 times [1.5; 1.9] vs. CT-2, CT-3 and CT-4 ($p < 0.001$) (Figure 6).

Selectins (cluster of differentiation 62, or CD62) are cell membrane glucoproteins, which ensure adhesion interactions between hematopoietic, tumour cells, white blood cells, platelets and endothelium. Cell adhesion has a crucial role to play in inflammatory, infectious, metastatic and immune processes, as well as in the ability of stem cells to identify their "niche" [22, 23]. Selectins are essential for rolling and adhesion of polymorphonucleocytes to endothelial wall, their migration to the intercellular matrix [24–26]. As we know, selectins are practically not expressed on membranes of non-activated cells. When endothelial cells, white blood cells and platelets are activated under specific conditions (changes in blood flow velocity, pH and temperature, impaired cell structure, exposure to biologically active molecules), their expression increases [22, 27]

E-selectin (E-sel) is expressed by endothelial cells when endothelium is damaged as well as in case of an inactive, long-lasting non-specific inflammation, promoting white blood attraction (chemotaxis) [24, 28, 29]. E-selectin is synthesised on endothelial cell membrane 4–6 hours after exposure to tumour necrosis factor α, interferon γ and interleukin-1. This selectin is involved in initiation of activated white cell adhesion to endothelial cells in the inflammation site [22, 30]. The highest selectin E concentrations can persist for 1–2 days. With lower levels, slow white cell rolling and inflammation severity drop. This molecule is involved in adhesion of endotheliocyte precursor, facilitating their migration and formation of capillaries. Introduction of an adenoviral vector of E-selectin promotes formation of capillaries and reduces severity of necrosis caused by ischaemia. Thus, E-selectin hyperexpression proves its involvement in adhesion of endothelial cell precursors and neoangiogenesis [22, 31, 32].

P-selectin (P-sel) is found in α-granules of platelets and secretory granules (Weibel-Palade bodies) of endothelial cells; they are involved in primary interaction between polymorphonuclear neutrophils and endothelial cells, particularly in the inflammation site. It has been proven that, when acting together with cytokines, it can regulate integrin synthesis. The highest concentration is observed 5–10 minutes after cell activation, and within half an hour/an hour P-selectin is detected on cell surfaces [22, 33]. According to G. V. Chaitanya et al., P-selectin expression can be regulated under the influence of nitrogen oxide [34, 35]. Besides, expression of this selectin on endothelial cell surface increases during hypoxia and reduces in hypoglycaemia [36].

L-selectin (L-sel) is involved in white cell migration to inflamed tissues; higher levels of L-selectin ligands initiate its expression. The important role of L-selectin is adhesion of circulating white blood cells to white blood cells adhering to a vessel wall, known as secondary binding. This selectin is constantly produced on white blood cells and quickly leaves the cell surface after its activation. It helps white cells to adhere to lymph node cells and activated endothelium [37, 38].

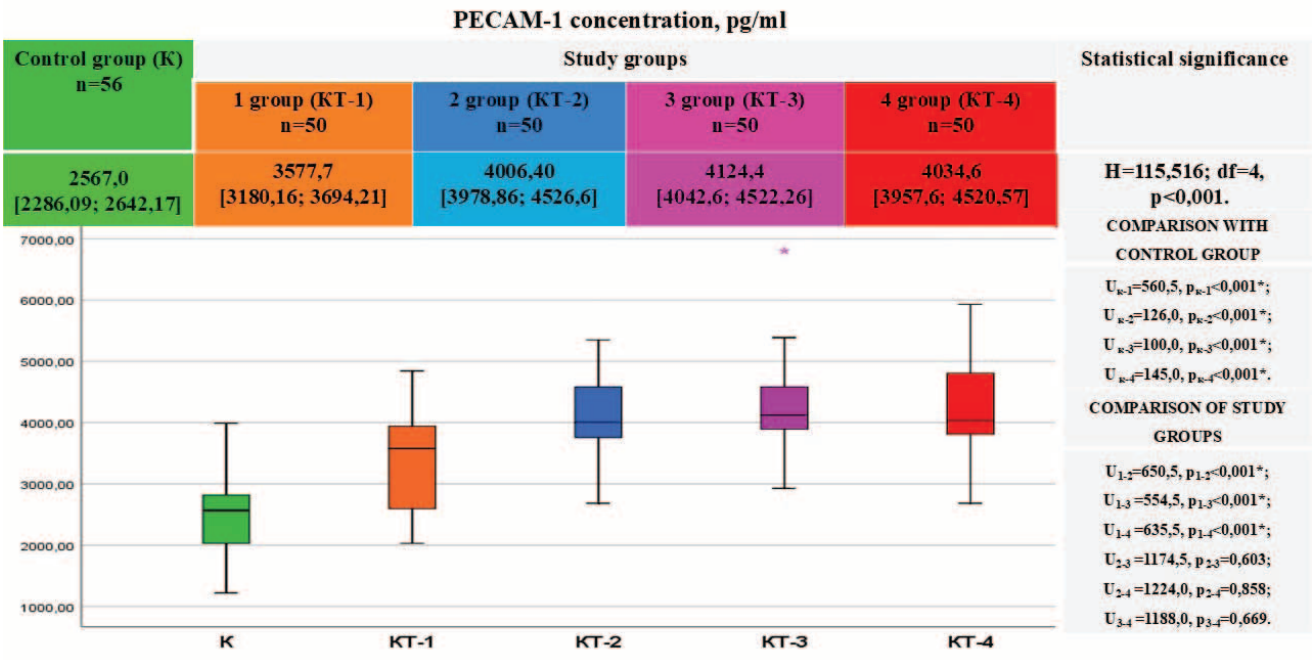

Figure 6. *The concentration of PECAM-1 intercellular adhesion molecules in the blood of patients in the studied groups*
Note: see figure 1

A study of E-selectin in patients after coronavirus infection showed higher concentrations in the study groups vs. controls: group 1 (CT-1) vs. controls — 1.5 times [2.4; 4.4] (p = 0.007); group 2 (CT-2) — 1.9 times [1.7; 4.8] (p < 0.001); group 3 (CT-3) — 1.8 times [1.5; 3.2] (p < 0.001), group 4 — (CT-4) — 1.7 times [1.6; 2.6] (p < 0.001) (Figure 7).

Analysis of P-selectin concentrations demonstrated similar results; its levels were higher in patients after COVID-19 as compared to controls. group 1 (CT-1) — 1.1 times [1.1; 1.9] (p = 0.002), group 2 (CT-2) — 1.7 times [1.4; 2.5] (p < 0.001), group 3 (CT-3) — 1.8 times [1.5; 2.5] (p < 0.001), in group 4 (CT-4) — 1.9 times [1.6; 2.8] (p < 0.001). Also, significantly higher levels of P-selectin were observed in patients with lung damage (CT-2, CT-3, CT-4) as compared to CT-1 patients: CT-2 vs. CT-1 — 1.5 times [1.01; 1.8] (p = 0.008), CT-1 and CT-3 — 1.6 times [1.02; 1.8] (p = 0.002), CT-4 and CT-1 — 1.7 times [1.1; 1.9] (p < 0.001) (Figure 8).

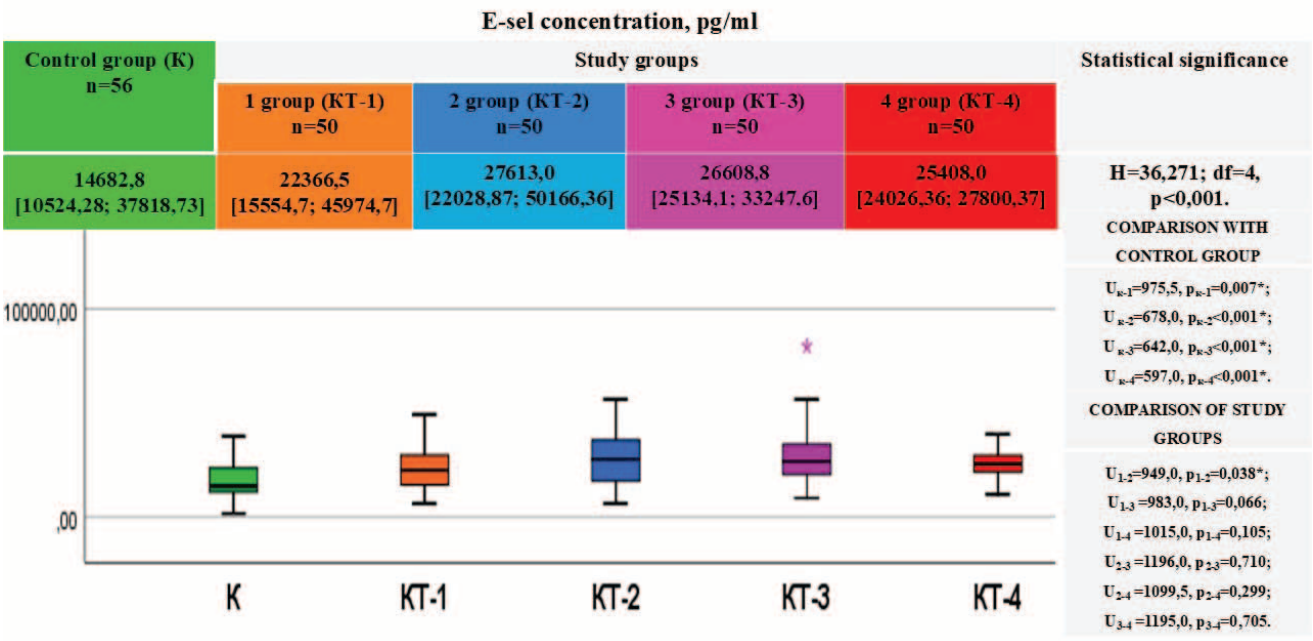

Figure 7. *The concentration of intercellular adhesion molecules of E-selectin in the blood of patients in the studied groups*
Note: see figure 1

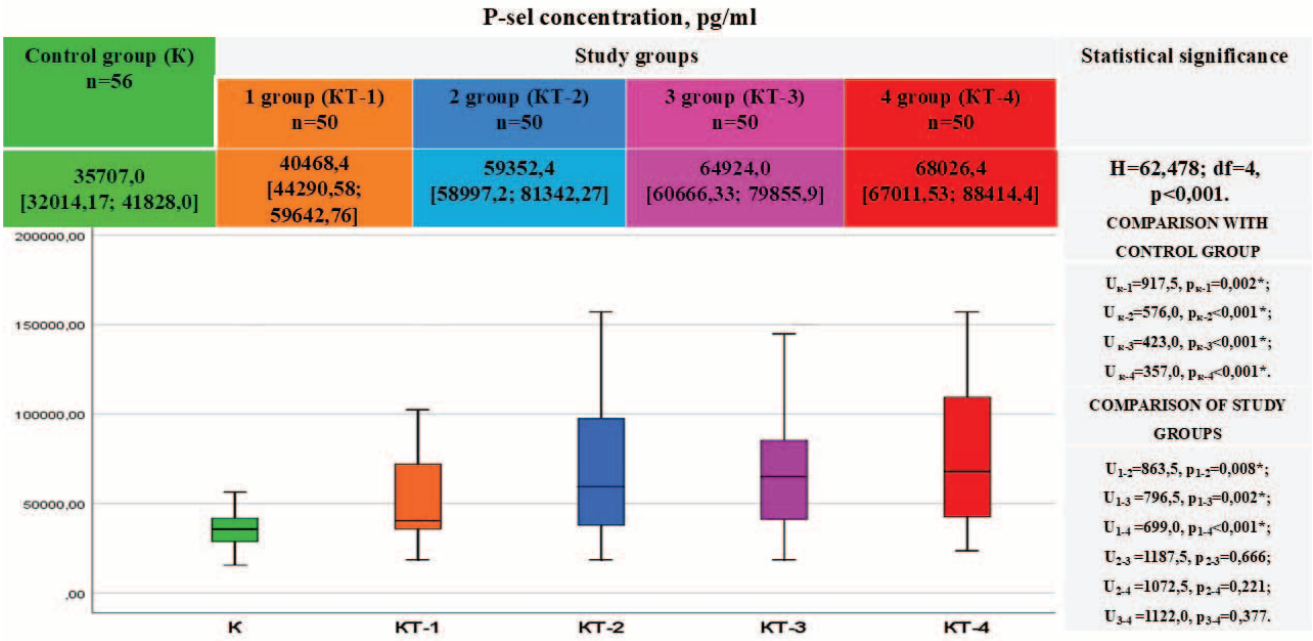

Figure 8. *The concentration of intercellular adhesion molecules of P-selectin in the blood of patients in the studied groups*
Note: see figure 1

An analysis of L-selectin levels in this study also demonstrated high concentrations in the study groups vs. controls: group 1 — 1.4 times [1.3; 1.7] ($p < 0.001$); group 2 — 1.2 times [1.1; 1.4] ($p < 0.001$); group 3 — 1.2 times [1.1; 1.5] ($p < 0.001$); group 4 — 1.2 times [1.4; 1.1] ($p = 0.001$). Excess concentrations of L-selectin were recorded in patients with CT-1 lung damage as compared to patients from CT-2, CT-3, CT-4 groups: CT-1 vs. CT-2 — 1.1 times [1.02; 1.4] ($p = 0.001$), CT-1 vs. CT-3 — 1.1 times [1.01; 1.3] ($p = 0.004$), CT-1 vs. CT-4 — 1.1 times [1.4; 1.05] ($p = 0.002$) (Figure 9).

EPCAM is a type I transmembrane glucoprotein; it plays an important role in cell adhesion and is expressed mainly in the large and small intestine, pancreas. Its intercellular binding is ensured by the extracellular domain of this protein; however, EPCAM-mediated intercellular contacts are relatively weak. EPCAM affects cadherin-mediated cell interaction by diminishing the association of the cadherin-catenin complex in cytoskeleton. Higher EPCAM expression lowers alpha catenin levels. Active proliferation in epithelial tissues is associated with increased EPCAM synthesis, whereas epithelial cell differentiation is associated with its decrease [39, 40]. This molecule possesses oncogenic potential: it can boost the activity of c-myc, e-fabp proteins, cyclins A and E and can be a marker of some cancer types due to specific expression only in epithelium and epithelial tumours [40].

A study of EPCAM showed its higher levels in patients with CT-1 lung damage as compared with controls: 1.6 times [1.2; 2] ($p < 0.001$). There are differences between study groups: mild lung damage (CT-1) and severe involvement (CT-3, CT-4) after the past coronavirus infection. EPCAM levels were 1.5 times higher when comparing CT-3 to CT-1 [1.01; 1.8] ($p = 0.007$) and 1.4 times higher when comparing CT-4 to CT-1 [1.03; 1.9] ($p = 0.005$) (Figure 10).

The available references evidence that COVID-19 patients have higher levels of soluble cell adhesion molecules, especially of ICAM-1 [41]. A retrospective study of COVID-19 patients in China showed that sICAM-1 concentrations in the blood increased with increasing disease severity. This parameter normalised during the recovery phase [42]. In patients with COVID-19 and cirrhosis, higher ICAM-1 levels were an independent predictor of death [43]. An analysis of blood ICAM-1 concentrations in COVID-19 patients 2 to 33 weeks after the diagnosis showed that ICAM-1 levels remained low two weeks after COVID-19 diagnosis and increased six-fold five weeks, and then normalised [42]. Similar data are available for ICAM-1 molecules in COVID-19 patients two weeks and five weeks after COVID-19 diagnosis: five weeks later, ICAM-1 levels increased six-fold vs. baseline values [42, 43].

In this study, plasma IAM levels were measured one month after discharge from a specialised hospital, and results are similar to the data presented by other authors, who studied the levels of endothelial dysfunction molecules at various stages after the past COVID-19 infection.

Following the study, a binary logistic analysis was performed in order to assess the influence (identification of independent predictive factors) of the test parameters on the probability of pulmonary fibrosis after COVID-19-associated lung damage. The model was based on the logistic regression method with sequential exclusion of the least significant factors. Selection and

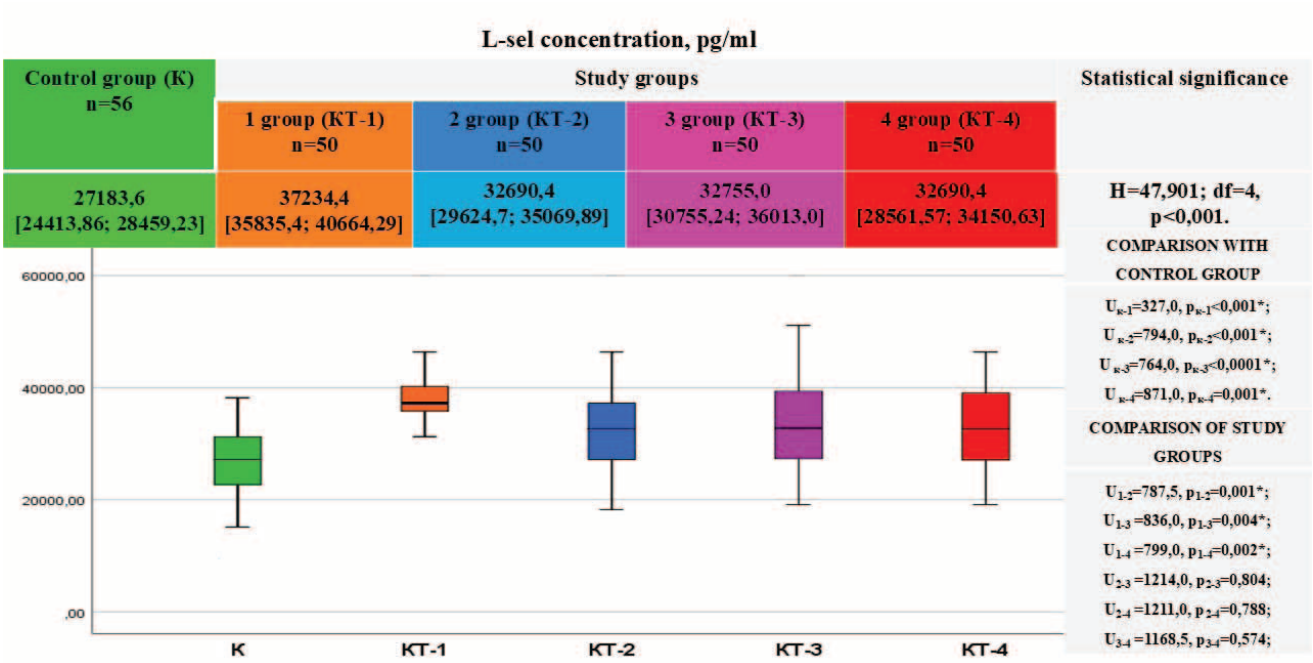

Figure 9. *The concentration of L-selectin intercellular adhesion molecules in the blood of patients in the studied groups*
Note: see figure 1

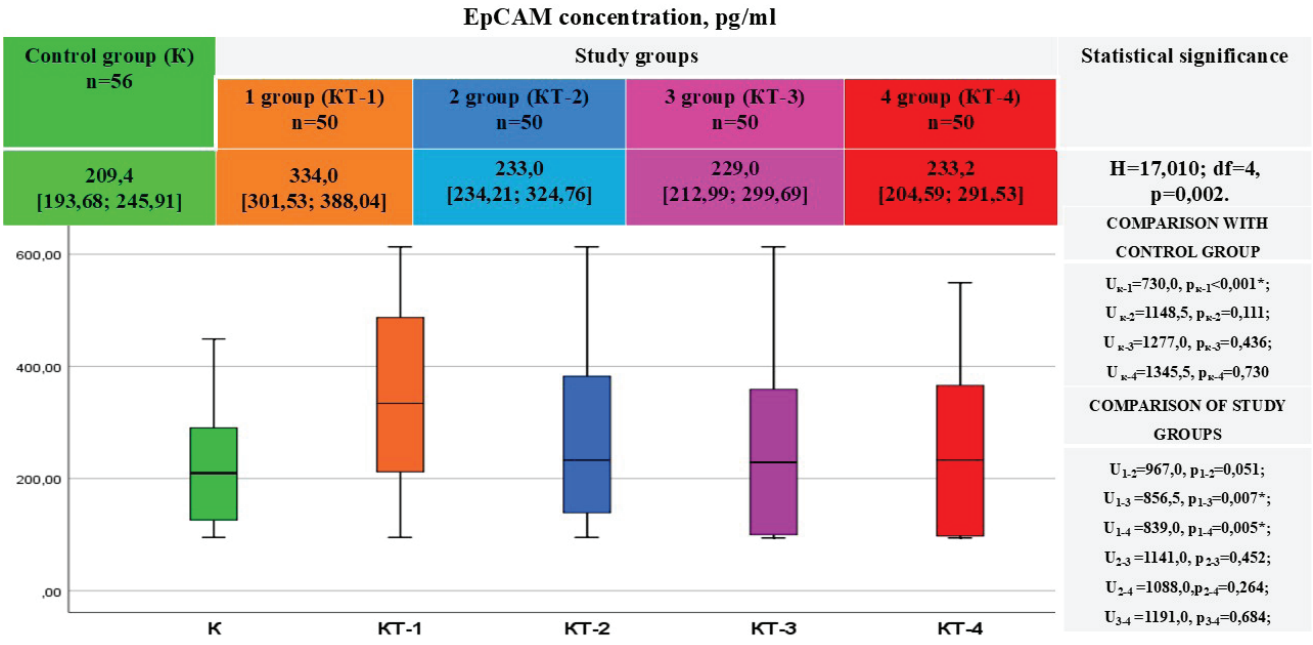

Figure 10. *The concentration of EPCAM intercellular adhesion molecules in the blood of patients in the study groups*
Note: see figure 1

the method of elimination were used to identify the factors with the highest confidence, including intercellular adhesion molecules. This model was converted into a calculator, which can be used in practical healthcare; and details will be provided later in publications.

Conclusions. Thus, patients with past coronavirus infection with lung involvement have higher concentrations of intercellular adhesion molecules from all superfamilies. Higher levels of intercellular adhesion molecules in study subjects prove the presence of endotheliosis and correlate with the degree of pulmonary tissue involvement, including recovery.

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