VASCULAR ENDOTHELIAL GROWTH FACTOR VEGF-A AS A MARKER OF ENDOTHELIAL DYSFUNCTION ASSOCIATED WITH THE SEVERE COURSE OF THE NEW CORONAVIRUS INFECTION COVID-19 IN PATIENTS WITH CONCOMITANT CHRONIC PATHOLOGY

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A prospective study was conducted of 163 patients with the new coronavirus infection COVID-19 hospitalized in the clinic of the Republican Specialized Scientific and Practical Medical Center of Epidemiology, Microbiology, Infectious and Parasitic Diseases and the Samarkand Regional Specialized Medical Center for the period 2020-2022, a study of the factor level was conducted vascular endothelial growth (VEGF A) in blood serum by enzyme immunoassay. Our studies have shown that the value of the marker of endothelial dysfunction, vascular endothelial growth factor VEGF-A, is related to gender, age, severity, and also depending on concomitant diseases. At the same time, monitoring indicators of inflammatory markers, endothelial dysfunction of the vascular endothelial growth factor VEGF-A are significant for identifying risk factors for the development of complications in cardiovascular diseases, both at the time of admission and in the period of early convalescence.
Ключевые слова: COVID 19, comorbidity, vascular endothelial growth factor (VEGF A), endothelial dysfunction

Background. The new coronavirus infection (COVID-19) currently remains a pressing medical and social problem: wave-like increases in the incidence rate are registered with varying frequency in all countries of the world. Over time, more and more attention is being paid to the consequences of COVID-19 – post-COVID syndrome, the manifestations of which are exacerbations of chronic diseases that persist for ≥12 weeks [1].

In COVID-19 patients with comorbidities, hypoxia and inflammation play an important role in stimulating the neovascularization process, which occurs in response to increased tissue oxygen demand, leading to the production of vascular endothelial growth factor VEGF-A. This mechanism provides a compensatory response that allows tissues to increase their oxygenation by inducing the growth of new vessels [2]. This may lead to increased concentrations of unbound forms of VEGF-A, which may act on other receptors, prolonging the disease process. SARS-CoV-2-infected individuals exhibit elevated plasma VEGF-A levels both during acute illness and convalescence, which may be responsible for diffuse microvascular injury. Several studies suggest that serum VEGF-A may also be a potential biomarker for long-term COVID-19, while evidence for COVID-19 vaccines is lacking and deserves further study [3]. During the convalescence period, many patients continue to experience shortness of breath, cough, fatigue, and blood pressure instability. Coronary heart disease and hepatobiliary pathology are risk factors for severe form in patients with COVID 19 [4]. Dysfunction of the endothelium plays an important role in the development and progression of the pathological process in the lungs and cardiovascular diseases in SARS-CoV-2 infection. Dysfunction of the endothelium is a common denominator between SARS-CoV-2 infection, previous comorbidities and age [5]. Comorbidities are a factor that increases the risk of adverse outcomes in COVID-19. Approximately 80% of COVID-19 patients with comorbidities experience severe disease [6]. Moreover, the most unfavorable outcomes in COVID-19 are most often associated with diseases such as arterial hypertension, coronary heart disease, chronic heart failure and diabetes mellitus [7]. Perhaps endothelial dysfunction is a link between these conditions, such as arterial hypertension and diabetes mellitus against the background of a new coronavirus infection [8]. Also, the risk of developing severe SARS-CoV-2 infection in individuals with obesity and diabetes is associated with underlying systemic inflammation and dysfunction of the immune system. In addition, this category of patients is more likely to experience post-COVID syndrome and worsen the course of

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chronic diseases [9, 10]. In this regard, studying the role of vascular endothelial growth factor VEGF-A as a marker of endothelial dysfunction is important in addressing issues of patient management in severe cases of the disease, in predicting unfavorable outcomes of COVID-19 in patients with concomitant chronic pathology.

The aim of the study was to study the relationship between the level of the endothelial dysfunction marker vascular endothelial growth factor VEGF-A and the severe course of COVID-19 in patients with chronic diseases.

Material and methods. A prospective study was conducted of 163 (100%) patients with a new coronavirus infection COVID-19 hospitalized in the clinics of the RSPMTSEMIPZ and the Samarkand Regional Specialized Medical Center for the period 2020-2022. Patients with moderate form of the disease accounted for 47.2% (n=77), with severe form – 52.8% (n=86), also female patients accounted for 52.1% (n=94), male patients – 42.3% (n=69). The average age of patients with severe form of the disease was 56.7±1.21 years, moderate form – 48.52±1.25 years. All patients had a positive PCR test result for RNA SARS-CoV-2 (Real-time Rotor-Gene, USA). The diagnosis of pneumonia was established during examination of the patient using instrumental methods (Toshiba Aquilion 32-slice CT, Japan). Pulse oximetry was performed with SpO2 measurement to detect respiratory failure and assess the severity of hypoxemia using finger pulse oximeters (Rudolf Riester GmbH, Germany). The level of interleukins IL1, IL6 and vascular endothelial growth factor (VEGF A) was determined in the blood serum by enzyme immunoassay using the test system of Cytokine LLC (RF) and Vector Best JSC (Novosibirsk, RF), according to the attached instructions, with standard values of 129.50±18.29 pg/ml. The hemostasis parameters were determined by the coagulometry method: D-dimer (quantitative method, mg/l). The coagulogram study was performed on an automatic analyzer-coagulometer CYANS mart (Instrumentation Laboratory Company, Werfen, USA) using reagents.

Laboratory markers of inflammation (procalcitonin, ferritin, CRP) were studied.

Statistical processing was carried out using the standard office software package Microsoft Excel 2019.

Results and discussion. Our studies have shown that the value of the endothelial dysfunction marker vascular endothelial growth factor VEGF-A is associated with gender, age and severity of the disease. We found that, along with a significant increase in the VEGF-A level in all patients, it was significantly higher in men over 55 years of age with coronavirus infection with a severe course of

Table 1

Indicators of vascular endothelial growth factor VEGF-A and inflammatory markers depending on gender in COVID-19 patients over 55 years of age

Indicator	Floor	Severe form n-86		Moderately severe form n-77	
		Admission day	Day of discharge	Admission day	Day of discharge
VEGF-A 129.50±18.29 pg/ml	Women Men	271.63±42.73* 407.97±56.22*•	357.36±50.06* 492.60±72.63*•	265.67±30.63* 244.72±51.73*•	209.79±25.37* 205.89±58.97*
Procalcitonin < 0.5 mcg/l	Women Men	2.43±0.50 4.23±1.07*	1.19±0.14 1.44±0.16	1.28±0.68 3.56±1.85	0.90±0.41 0.84±0.47
IL-1 up to 4.9 pg/ml	Women Men	31.46±5.31* 44.33±6.51*•	19.62±3.36* 28.48±5.19*•	26.98±6.43* 17.75±5.04*•	17.94±2.53* 16.08±2.88*
IL-6 up to 7.0 pg/ml	Women Men	41.92±10.78* 50.58±9.90*•	33.40±6.55* 23.34±2.96*•	38.50±6.17* 46.91±26.98*	8.43±1.84* 14.05±5.10*
CRP-5 mg/l	Women Men	35.99±4.85* 27.18±2.35*•	20.88±3.59* 16.91±1.60*•	19.12±1.71* 17.63±1.50*	21.47±1.54* 6.88±1.99*•
Ferritin – male 20-250 mcg/l, female 10-120 mcg/l	Women Men	370.53±42.01* 427.78±51.26*•	332.0±38.51* 341.57±3.40*•	177.19±22.99* 159.33±30.33*•	135.05±13.29* 106.73±6.56•*

Note: * - P<0.05 is reliable relative to the corresponding indicators for severity of the disease; • - P<0.05 is reliable relative to the corresponding indicators depending on gender.

the disease, both upon admission (407.97±56.22 pg/ml relative to the indicators in women 271.63±42.73 pg/ml) and upon discharge (492.60±72.63 relative to 357.36±50.06 pg/ml, P<0.05). The same dynamics were revealed in the IL1 indices (44.33±6.51 and 28.48±5.19 relative to the indices of women 31.46±5.31 and 19.62±3.36 upon admission and discharge, respectively), IL6 (50.58±9.90 and 23.34±2.96 relative to the indices of women 41.92±10.78 and 19.62±3.36 upon admission and discharge, respectively), ferritin – in males they are significantly higher than in females, both upon admission and upon discharge (427.78±51.26 relative to the values in women 370.53±42.01 and 341.57±38.40 relative to 308.96±30.44 μg/l, P<0.05) (Tab. 1).

In the dynamics of the disease, the same direction of change in the level of inflammation markers was noted – in the dynamics towards discharge, there was a tendency towards normalization and a decrease in all indicators, with the exception of the level of the endothelial dysfunction marker vascular endothelial growth factor VEGF-A, which continued to increase in severe cases and slightly decrease in moderate cases of the disease, significantly exceeding the control indicators in all patients at the significance level (P≤0.05). We also studied the nature of the dynamics of the vascular endothelial growth factor VEGF-A indicator in the patients we examined, depending on concomitant diseases. All patients with chronic comorbidities have endothelial dysfunction. Patients with comorbidity against the background of COVID 19 increase the risk of an unfavorable outcome due to decompensation of chronic concomitant pathology and the development of acute complications. When analyzing markers of endothelial dysfunction VEGF-A in the patients we examined (n=163) with concomitant diseases such as coronary heart disease (CHD), arterial hypertension (AH), anemia, diabetes mellitus (DM), chronic pyelonephritis (CP) and obesity, a high level of this indicator was revealed (Tab. 2).

Table 2

Indicators of vascular endothelial growth factor VEGF-A in COVID-19 patients depending on concomitant pathology

Associated pathology	Severe form n-86 VEGF 129.50±18.29 pg/ml		Moderately severe form n-77 VEGF 129.50±18.29 pg/ml	
	Admission day	Day of discharge	Admission day	Day of discharge
Ischemic heart disease	615.25±53.17	675.06±53.70	405.00±30.76*	353.58±30.82*
Arterial hypertension	576.24±60.44	651.66±66.52	354.10±38.41*	316.21±33.20*
Obesity	457.76±68.84	547.88±89.99	528.74±14.49	457.03±90.12*
Diabetes mellitus	665.77±108.97	737.71±100.11	227.35±45.15	132.50±11.30*
Anemia	351.17±34.65	427.36±42.99	289.36±37.06	268.24±27.36*
Bronchial asthma	592.25±132.60	656.69±125.81	361.95±32.94	307.84±27.18*
Chronic pyelonephritis	638.08±95.05	697.56±117.72	267.48±85.67*	233.87±77.14 *

Note: *- P<0.05 significant difference in indicators relative to indicators of severe course of the disease.

Statistical analysis of the dynamics of vascular endothelial growth factor VEGF-A in the above-described diseases of the patients examined by us showed reliably high rates in patients with severe disease. Thus, in patients with severe course of the disease in ischemic heart disease, the values of vascular endothelial growth factor VEGF-A both at admission and at discharge are significantly higher than in patients with moderate course (615.25±53.17 relative to 405.00±30.76 pg/ml and 675.06±53.70 relative to 353.58±30.82 pg/ml, respectively), diabetes mellitus in patients with severe (665.77±108.97 and 737.71±100.11) and moderate (227.35±45.15 and 132.50±11.30) and arterial hypertension (AH) (576.24±60.44 relative to 354.10±38.41 pg/ml and 651.66±66.52 relative to 316.21±33.20 pg/ml, respectively), chronic pyelonephritis (638.08±95.05 relative to 267.48±85.67 pg/ml and 697.56±117.72 relative to 233.87±77.14 pg/ml, respectively), in patients with bronchial asthma (BA) and anemia, reliable differences were noted upon discharge from the

hospital (592.25±132.60 and 656.69±125.81) and (351.17±34.65 and 427.36±42.99, respectively) (Table 2).

Thus, in patients with such concomitant diseases as coronary heart disease (CHD), arterial hypertension (AH), diabetes mellitus (DM), chronic pyelonephritis (CP), bronchial asthma, obesity and anemia, high rates of endothelial dysfunction of vascular endothelial growth factor VEGF-A were detected both in the acute period, and an increase in values was especially noted at the time of discharge. The study shows that at the time of discharge from the hospital, patients experienced an exacerbation of chronic concomitant diseases requiring correction of drug therapy.

We analyzed the dynamics and relationship of inflammation markers, coagulation with the marker of endothelial dysfunction vascular endothelial growth factor VEGF-A in the patients we examined with coronary heart disease (CHD) and without CHD. A comparison was made of the indices of endothelial dysfunction of vascular endothelial growth factor VEGF-A, inflammation markers and coagulation indices in patients (n-64) at the time of discharge, i.e. during the period of early convalescence, taking into account the presence or absence of coronary heart disease (CHD) (Tab. 3).

Table 3

Indicators of markers of inflammation, coagulation and endothelial dysfunction of vascular endothelial growth factor VEGF-A in patients at the time of discharge with COVID-19 depending on the presence of coronary heart disease

Показатель	**Presence of IHD (n=35)**	**No ischemic heart disease (n=29)**
VEGF-A 129.50±18.29 pg/ml	555.66±67.58	427.36±152.99*
D-dimer <250 ng/l	595.42±123.65	490.79±68.75*
CRP-5 mg/l	22.30±2.27	18.26±1.62*
Procalcitonin, <0.5 mcg/l	0.59±0.08	0.50±0.08
Ferritin – male 20-250 mcg/l, female 10-120 mcg/l	258.37±28.08	295.05±47.62*
IL-1, up to 4.9 pg/ml	32.76±5.34	25.28±4.85*
IL-6, up to 7.0 pg/ml	14.63±4.21	9.54±2.37*

Note: P<0.05 indicates a significant difference in indicators relative to indicators in the group with coronary heart disease.

Despite significant differences between the groups, a positive direction of changes was noted in the dynamics of most indicators (a significant decrease in indicators relative to values upon admission was noted) (D-dimer, procalcitonin, ferritin) (Table 3). However, the level of vascular endothelial growth factor VEGF-A (555.66±67.58 and 427.36±152.99 pg/ml, respectively, P<0.05), CRP (22.30±2.27 and 18.26±1.62 mg/l, respectively, P<0.05), cytokines (IL1- 32.76±5.34 and 25.28±4.85 pg/ml, respectively; IL6-1 14.63±4.21 and 9.54±2.37 pg/ml, respectively, P<0.05) at the time of discharge, i.e. during the early convalescence period, were significantly higher than the reference values in the group of patients with coronary artery disease.

Conclusion. An increase in the plasma concentration of vascular endothelial growth factor VEGF-A reflects the progression of endothelial dysfunction, one of the key links in the pathogenesis of COVID-19. Determination of vascular endothelial growth factor VEGF-A in blood plasma in patients with concomitant pathology is of diagnostic value in terms of predicting the risk of severe COVID-19 and its long-term consequences. The study revealed that increased levels of vascular endothelial growth factor VEGF-A and inflammation markers were observed in male patients over 50 years of age with severe disease. It can be concluded that the severe course of COVID-19 in individuals with chronic pathology is associated with endothelial dysfunction, which indicates the likely development of an unfavorable outcome of the disease during the recovery period. At the same time, monitoring of inflammation markers, endothelial dysfunction, and vascular endothelial growth factor VEGF-A are significant for identifying risk factors for the development of complications in cardiovascular diseases both at the time of admission and after discharge from the

hospital. It should be noted that there may be a high probability of exacerbation of chronic diseases in the context of stable endotheliopathy, which requires the need to prescribe endothelial protective therapy to patients with COVID-19 during the recovery period.

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РЕЗЮМЕ

ФАКТОР РОСТА ЭНДОТЕЛИЯ СОСУДОВ VEGF-A КАК МАРКЕР ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ, АССОЦИИРОВАННОЙ С ТЯЖЕЛЫМ ТЕЧЕНИЕМ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ COVID-19 У ПАЦИЕНТОВ С СОПУТСТВУЮЩЕЙ ХРОНИЧЕСКОЙ ПАТОЛОГИЕЙ

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Проведено проспективное исследование 163 пациентов с новой коронавирусной инфекцией COVID-19, госпитализированных в клинику Республиканского специализированного научно-практического медицинского центра эпидемиологии, микробиологии, инфекционных и паразитарных заболеваний и Самаркандского областного специализированного медицинского центра за период 2020-2022 годы, проведено исследование уровня фактора роста эндотелия сосудов (VEGF A) в сыворотке крови методом иммуноферментного анализа. Наши исследования показали, что значение маркера эндотелиальной дисфункции – сосудистого эндотелиального фактора роста VEGF-A – связано с полом, возрастом, степенью тяжести заболевания, а также зависит от сопутствующих заболеваний. При этом мониторинг показателей маркеров воспаления – эндотелиальной дисфункции сосудистого эндотелиального фактора роста VEGF-A – имеет значение для выявления факторов риска развития осложнений сердечно-сосудистых заболеваний как на момент поступления, так и в период ранней реконвалесценции.

Ключевые слова: COVID-19, коморбидность, сосудистый эндотелиальный фактор роста (VEGF A), эндотелиальная дисфункция

XÜLASƏ

YANAŞI XRONIKI PATOLOGIYASI OLAN XƏSTƏLƏRDƏ COVID-19-UN AĞIR GEDIŞI ILƏ ASSOSIASIYA OLUNAN ENDOTEL DISFUNKSIYASININ MARKERI KIMI DAMAR ENDOTELIAL BÖYÜMƏ FAKTORU VEGF-A-NIN ƏHƏMIYYƏTI

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2020-2022-ci illər ərzində yeni koronavirus infeksiyası (COVID-19) ilə xəstəxanaya yerləşdirilmiş 163 xəstə arasında prospektiv tədqiqat aparılmışdır. Epidemiologiya, mikrobiologiya, yoluxucu və parazitar xəstəliklər üzrə Respublika Xüsusiləşdirilmiş Elmi-Praktiki Tibb Mərkəzi və Səmərqənd Vilayət Xüsusiləşdirilmiş Tibb Mərkəzinin klinikalarında aparılan bu tədqiqatda serumda damar endotelial böyümə faktorunun (VEGF-A) səviyyəsi immunoferment analiz metodu ilə müəyyən edilmişdir. Araşdırmamız göstərmişdir ki, endotelial disfunksiya markerinin — damar endotelial böyümə faktoru VEGF-A-nın səviyyəsi xəstənin cinsi, yaşı, xəstəliyin ağırlıq dərəcəsi və yanaşı xəstəliklərin mövcudluğu ilə əlaqəlidir. Bundan əlavə, iltihab markerlərinin və endotelial disfunksiya göstəricisi olan VEGF-A faktorunun monitorinqi həm xəstənin xəstəxanaya qəbul olunduğu anda, həm də erkən rekonvalessensiya dövründə ürək-damar fəsadlarının inkişafı üçün risk faktorlarını müəyyən etmək baxımından əhəmiyyətlidir.
Açar sözlər: COVID-19, komorbidlik, damar endotelial böyümə faktoru (VEGF-A), endotelial disfunksiya

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