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Analysis of the relationship between low-grade inflammation markers and the severity of atherosclerotic coronary bed lesions

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ABSTRACT

Aim. To study serum concentrations of low-grade inflammation markers and the severity of atherosclerotic processes in the coronary artery in patients with coronary heart disease (CHD) in the context of their clinical and instrumental characteristics.

Materials and methods. The study included 264 participants (161 men and 103 women), with 220 of them being diagnosed with CHD. Subgroups were identified among the participants, including those with a history of myocardial infarction (110 patients) and angina pectoris (152 patients). A control group consisted of healthy volunteers (44 persons). The patients underwent coronary angiography, echocardiography, duplex ultrasound scanning of the extracranial segments of the brachiocephalic arteries. The level of C-reactive protein (CRP (mg / l)), tumor necrosis factor alpha (TNFα (pg/ml)), growth differentiation factor 15 (GDF-15 (pg/ml)), and endothelial cell specific molecule-1 (ESM-1 (ng/ml)) in the blood serum were measured. Statistical significance was considered at $p < 0.05$.

Results. A significantly higher concentration of all laboratory markers of low-grade inflammation in the CHD group of patients compared to the control group, as well as a significant increase in their values with enhanced severity of coronary atherosclerosis ($p < 0.0001$) was found. Significant differences in marker levels were also found between patients with angina pectoris and a history of myocardial infarction compared to those without these conditions. A correlation was revealed between the value of markers and various clinical and instrumental characteristics of the patients. Multivariate linear regression analysis revealed a statistically significant association of SYNTAX score with the concentration of GDF-15 and ESM-1, but not with CRP and TNFα.

Conclusion. The simultaneous measurement of multiple laboratory parameters may be a more effective method for assessing the risk of CHD progression. The study also showed that endocan and GDF-15 have high prognostic significance in evaluating the severity of atherosclerotic processes in the coronary arteries.

Keywords: inflammation, C-reactive protein, tumor necrosis factor alpha, growth differentiation factor 15, specific molecule of endothelial cells-1, endocan, atherosclerosis, coronary heart disease

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Анализ взаимосвязи маркеров низкоинтенсивного воспаления с выраженностью атеросклеротического поражения коронарного русла

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РЕЗЮМЕ

Цель. Изучение сывороточных концентраций маркеров низкоинтенсивного воспаления у пациентов с ишемической болезнью сердца (ИБС) в контексте их клинико-инструментальных характеристик, а также оценка их предиктивной ценности в выраженности атеросклеротических процессов коронарного русла.

Материалы и методы. В исследование включены 264 человека (161 мужчина и 103 женщины), из них 220 – пациенты с диагнозом ИБС. Среди пациентов были выделены подгруппы с наличием инфаркта миокарда в анамнезе (110 человек) и стенокардией (152 человека). Группа контроля представлена здоровыми добровольцами (44 человека). Пациентам выполнены коронароангиография; эхокардиографическое исследование; дуплексное ультразвуковое сканирование внечерепных отделов брахиоцефальных артерий. Проведено исследование уровня С-реактивного белка (СРБ, мг/л), фактора некроза опухоли альфа (ФНО-α, пг/мл), фактора дифференцировки роста 15 (GDF-15, пг/мл) и специфической молекулы эндотелиальных клеток-1 (ESM-1, нг/мл) в сыворотке крови. Статистически значимыми считали различия при $p < 0,05$.

Результаты. Выявлена значимо большая концентрация всех лабораторных маркеров субклинического воспаления в группе пациентов с ИБС в сравнении с контролем, а также значимое повышение их значений по мере увеличения выраженности коронарного атеросклероза ($p < 0,0001$). Показана статистическая значимость различий уровня маркеров между группами пациентов с наличием стенокардии и инфаркта миокарда в анамнезе в сравнении с пациентами без данных признаков. Выявлена корреляционная связь разной силы и значимости между значением маркеров и рядом клинико-инструментальных характеристик пациентов. При проведении линейного многофакторного регрессионного анализа выявлена статистически значимая связь баллов по шкале SYNTAX с концентрацией GDF-15 и ESM-1 при отсутствии таковой с СРБ и ФНО-α.

Заключение. Одновременное количественное определение нескольких лабораторных показателей может быть более мощным инструментом для оценки риска прогрессирования ИБС. Показано, что эндокан и GDF-15 имеют высокую предиктивную значимость в оценке выраженности атеросклеротических процессов в коронарных артериях.

Ключевые слова: воспаление, С-реактивный белок, фактор некроза опухоли альфа, фактор дифференцировки роста 15, специфическая молекула эндотелиальных клеток-1, эндокан, атеросклероз, ишемическая болезнь сердца

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

In recent years, inflammation has been recognized as a critical component in the pathogenesis of cardiovascular diseases. Numerous studies have explained the complex relationship between inflammation and coronary heart disease (CHD) [1]. Chronic low-grade inflammation, in particular, has been recognized as a factor contributing to the onset and progression of various cardiovascular diseases, including atherosclerosis, acute coronary syndrome, and heart failure [1]. Moreover, arterial hypertension, dyslipidemia, diabetes, and obesity are associated with low-grade inflammatory processes [2].

Numerous studies have demonstrated the role of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNFα) as markers of low-grade inflammation in diseases of the circulatory system [1–7]. There are also isolated studies devoted to the study of a similar role of such indicators as growth differentiation factor 15 (GDF-15) and endothelial cell specific molecule-1, or endocan (endothelial cell specific molecule-1, ESM-1) [8–11].

GDF-15, a member of the transforming growth factor beta superfamily, is a marker of inflammation and apoptosis of cells, primarily atypical ones. Its expression is induced in macrophages by interleukin-1 and TNFα, leading to inhibition of both their activation and the inflammatory reaction itself [8]. In turn, a number of studies have shown that ESM-1, being a surrogate marker of inflammation and endothelial dysfunction, plays a crucial role in the processes of angiogenesis, inflammation, and vascular permeability [11].

As evidenced by the foregoing, it seems relevant to study the relationship between serum concentrations of the listed laboratory markers in patients with CHD and to assess their predictive ability in the progression of coronary atherosclerosis.

The aim of the study was to investigate the relationship between serum concentrations of low-grade inflammation markers and the severity of atherosclerotic processes in the coronary bed in patients with CHD in the context of their clinical and instrumental characteristics.

MATERIALS AND METHODS

The inclusion criterion for the patients into the study was the presence of clinically and instrumentally verified CHD. *The exclusion criteria* were: myocardial infarction (MI) or stroke occurred within the past 6 weeks; any acute and chronic inflammatory diseases that can affect serum concentrations of CRP, TNFα, GDF-15 and ESM-1; chronic kidney disease ≥ stage III (glomerular filtration rate <60 ml/min/1.73 m^2); primary and secondary cardiomyopathy, inflammatory heart diseases; oncological diseases, blood diseases and immune system diseases; pregnancy or lactation; mental disorders that hinder the contact with the patient during the cancer; and violation of the protocol or patient's refusal to participate in the study.

A total of 264 people (161 men and 103 women) were enrolled in this study, including 220 patients with an established diagnosis of CHD and 44 healthy volunteers (the control group).

All patients underwent coronary angiography using the General Electric Optima IGS 330 angiographic system. The SYNTAX score, an online calculator (https://officialsyntaxscore.com), was used for an objective quantitative assessment of the severity of atherosclerotic lesions in coronary arteries (CA). Considering that this score is a reliable tool for determining the severity of CA atherosclerosis, all patients were divided into the following groups: Group 1 – with moderate atherosclerotic CA lesions, having a SYNTAX score of 22 or less (124 patients); Group 2 – with severe CA atherosclerosis, having a score of 23–32 (53 patients); Group 3 – with extremely severe CA lesions, having a score of 33 or more (43 patients). Among the participants with CHD, several subgroups were identified: patients who underwent percutaneous coronary intervention (stenting) within the past 4 months to 6 years – 45 persons, patients with multifocal atherosclerosis (MFA) – 46 persons, patients with a history of MI –110 persons, and patients with angina pectoris – 152 persons. The control group (Group 4) consisted of 44 healthy volunteers, in whom cardiovascular pathology was excluded due

to the absence of any clinical, anamnestic, or electrocardiographic signs of heart disease. All groups were comparable in terms of sex and age.

Echocardiographic examination (EchoCG) was performed using the Samsung Accuvix A30 ultrasound scanner (Samsung-Medison, South Korea), using two-dimensional EchoCG, Doppler EchoCG in pulsed and continuous wave modes, and color Doppler scanning. Standard structural parameters of the ventricles and atria, contractile and diastolic function of the left ventricle (LV), and valvular apparatus competency were evaluated. The intima-media thickness (IMT) was measured using duplex ultrasound scanning of the extracranial sections of the brachiocephalic arteries with the Samsung UGEO H60 ultrasound scanner (Samsung-Medison, South Korea).

The study of the concentrations of CRP, TNFα, GDF-15, and ESM-1 in the blood serum was also performed. For this purpose, venous blood was collected on an empty stomach before coronary angiography. Commercial test systems manufactured by Cloud Clone, USA (TNFα, pg/ml; GDF-15, pg/ml), Biomerica, USA (CRP, mg/l), and Aviscera, USA (ESM-1, ng/ml) were used.

The statistical processing of the study results was carried out using the STATISTICA 12.0 and MedStat programs. The data were presented as a median (Me) and interquartile interval (Q – 25th and 75th percentiles). The Mann-Whitney U-test was used to test statistical hypotheses when comparing two independent groups. The Kruskal – Wallis test was used for multiple comparisons in independent samples for quantitative or ordinal data. The Mann – Whitney test with the Bonferroni correction was used as a posteriori criterion for pairwise comparisons. The multiple comparisons of the proportions of nominal features in independent samples were performed using the Pearson's chi-square test. The Marascuilo procedure was used as a posteriori criterion for pairwise comparisons. The statistical relationship between two features was measured using Spearman's rank correlation. The multivariate linear regression analysis was performed to estimate the dependence of atherosclerotic lesions in the CAs according to the SYNTAX score on laboratory parameters of low-grade inflammation. The critical significance level p for all used analysis procedures was set at 0.05.

RESULTS

The clinical, anamnestic, and laboratory-instrumental characteristics of the patients enrolled in the study are presented in Table 1.

Table 1

Clinical, anamnestic, and laboratory-instrumental characteristics of the patients

Parameter	Group 1, $n = 124$	Group 2, $n = 53$	Group 3, $n = 43$	p	p_{1-2}	p_{1-3}	p_{2-3}
Age (years), *Me* (Q_{25}; Q_{75})	64.0 [58.0; 69.0]	66.0 [60.0; 70.0]	66.0 [60.0; 70.0]	0.882	0.961	0.778	1.000
SYNTAX, (score), *Me* (Q_{25}; Q_{75})	12.25 [5.0; 17.0]	27.5 [24.0; 29.5]	36.25 [34.0; 40.5]	<0.001	<0.001	<0.001	<0.001
LVEF, %, *Me* (Q_{25}; Q_{75})	57.0 [49.0; 62.0]	54.0 [47.0; 59.0]	52.0 [44.0; 59.0]	0.063	0.419	0.091	1.000
Angina, *n* (%)	73 (58.9)	42 (79.2)	37 (86.0)	0.004	0.063	0.026	0.973
Angina class 2, *n* (%)	25 (20.2)	12 (22.6)	6 (14)	0.547	–	–	–
Angina class, 3 *n* (%)	49 (39.5)	29 (54.7)	27 (62.8)	0.016	0.237	0.047	0.840
Angina class 4, *n* (%)	–	–	4 (9.3)	<0.001	1.000	0.039	0.174
NYHA class II, *n* (%)	44 (35.5)	14 (26.4)	6 (14.0)	0.110	–	–	–
NYHA class III, *n* (%)	80 (64.5)	39 (73.6)	31 (72.0)	0.793	–	–	–
NYHA class IV, *n* (%)	–	–	6 (14.0)	<0.001	1.000	0.003	0.033
History of MI, *n* (%)	45 (36.3)	41 (77.4)	25 (58.1)	<0.001	<0.001	0.069	0.198
IMT, cm, *Me* (Q_{25}; Q_{75})	0.8 [0.8; 0.9]	1.05 [0.9; 1.1]	0.9 [0.8; 1.0]	0.024	0.030	0.641	0.972

Note. IMT – intima-media thickness; LVEF – left ventricular ejection fraction; MI – myocardial infarction.

The study revealed a significantly higher concentration of all laboratory markers of low-grade inflammation in patients with CHD compared to the control group (Table 2).

When examining the levels of laboratory markers in the blood serum of patients in three groups according to the SYNTAX score, a statistically significant enhance in the concentration of CRP, TNFα, GDF-15, and ESM-1 was found as the severity of coronary atherosclerosis increased (Table 3).

It is necessary to note the statistical significance of the differences in the concentration of low-grade inflammation markers in the blood serum depending on the presence of certain clinical signs (Tables 4, 5).

Also noteworthy are the discovered correlations between the concentration of low-grade inflammation markers in the blood serum and several clinical and instrumental indicators (Table 6).

Table 2

Laboratory values in patients with coronary heart disease and the control group

Parameter	Patients with CHD (n = 220)	Control group (n = 44)	p
CRP, mg/l	7.73 [6.29; 9.21]	3.22 [2.15; 3.76]	<0.001
TNFα, pg/ml	4.6 [3.6; 5.8]	1.4 [1.1; 2.7]	<0.001
GDF-15, pg/ml	723 [579; 912]	405 [291; 591]	<0.001
ESM-1, ng/ml	18.95 [11.51; 26.13]	5.97 [4.38; 8.25]	<0.001

Table 3

Laboratory values in patients of three groups

Parameter	Group 1 (n = 124)	Group 2 (n = 53)	Group 3 (n = 43)	p	p_{1-2}	p_{1-3}	p_{2-3}
CRP, mg/l	7.23 [5.64; 7.86]	8.49 [7.99; 9.15]	9.99 [9.32; 11.63]	<0.001	<0.001	<0.001	0.023
TNFα, pg/ml	4.0 [3.2; 4.8]	5.5 [4.7; 5.9]	7.05 [5.2; 7.8]	<0.001	<0.001	<0.001	0.102
GDF-15, pg/ml	613.0 [422.5; 695.5]	891.0 [800; 944]	1245.0 [1100; 1400]	<0.001	<0.001	<0.001	<0.001
ESM-1, ng/ml	14.40 [10.19; 19.91]	20.31 [12.75; 24.12]	32.10 [22.12; 38.21]	<0.001	0.039	<0.001	<0.001

Note. The Kruskal–Wallis test was used for comparisons of the quantitative or ordinal data.

Table 4

Laboratory values in patients depending on the presence of angina

Parameter	Patients with angina (n = 152)	Patients without angina (n = 68)	p
CRP, mg/l	8.15 [6.84; 9.56]	7.44 [5.24; 8.12]	0.003
TNFα, pg/ml	5.0 [3.8; 6.1]	4.2 [3.4; 5.4]	0.006
GDF-15, pg/ml	789 [632; 979]	656.5 [500; 842]	<0.001
ESM-1, ng/ml	20.05 [13.38; 29.57]	13.29 [9.23; 20.05]	<0.001

Table 5

Laboratory values in patients depending on the presence of a history of myocardial infarction

Parameter	Patients with history of MI (n = 110)	Patients without history of MI (n = 110)	p
CRP, mg/l	8.33 [6.89; 9.32]	7.44 [6.21; 8.45]	0.039
TNFα, pg/ml	5.1 [3.9; 6.1]	4.3 [3.3; 5.4]	0.004
GDF-15, pg/ml	866 [690; 980]	633 [497; 800]	<0.001
ESM-1, ng/ml	20.605 [14.78; 30.10]	12.105 [6.78; 19.21]	<0.001

Table 6

Evaluation of statistical relationships between clinical, instrumental, and laboratory parameters using the Spearman's *R* rank correlation coefficient

Parameter	R (p-value)			
	CRP	TNFα	GDF-15	ESM-1
SYNTAX score	+0.487 (<0.001)	+0.573 (<0.001)	–0.830 (<0.001)	+0.474 (<0.001)
IMT	+0.178 (0.184)	+0.288 (0.030)	–0.499 (<0.001)	+0.436 (<0.001)
LVEF	–0.092 (0.174)	–0.125 (0.064)	–0.210 (0.002)	–0.197 (0.003)
FC of angina	+0.236 (<0.001)	+0.233 (<0.001)	+0.434 (<0.001)	+0.443 (<0.001)
FCHF by NYHA	+0.153 (0.023)	+0.220 (<0.001)	+0.307 (<0.001)	+0.110 (0.106)
Mounts passed after MI	+0.222 (0.625)	+0.198 (0.102)	+0.367 (0.683)	+0.261 (0.270)

Note. HF – heart failure.

The multivariate linear regression analysis was performed to estimate the dependence of the atherosclerotic lesions of the CAs according to SYNTAX score on laboratory indices of low-grade inflammation. This model was shown to be acceptable for prediction. This is evidenced by the highly significant value of the Fisher's criterion: $F = 76.138$ ($p < 0.00001$). The multiple correlation coefficient was 0.7686, while the adjusted determination coefficient was 0.5830. The Durbin – Watson coefficient was 1.9168, which is close to 2 and indicates the absence of autocorrelation in the residuals and the adequacy of the constructed model.

While analyzing the regression results, it should be noted that among the measured laboratory markers, a statistically significant relationship between the SYNTAX score was found only for GDF-15 and, to a lesser extent, for ESM-1 (Table 7), in contrast to CRP and TNFα.

Subsequently, after recalculating everything with the inclusion of only two indicators (GDF-15 and ESM-1), the model still appears acceptable for forecasting, The Fisher's criterion value was $F = 126.30$, ($p < 0.00001$); the multiple correlation coefficient was 0.7358; the adjusted coefficient of determination was 0.5371; and the Durbin – Watson coefficient was 1.9605.

Table 7

Results of the multivariate linear regression analysis of the relationship between SYNTAX score and laboratory parameters

Parameter	β	Standard error β	*b*	Standard error *b*	*p*
Intercept	–	–	–6.00057	1.694136	0.000489
GDF-15, pg/ml	0.650666	0.051819	0.02600	0.002070	<0.000001
ESM-1, ng/ml	0.136217	0.049111	0.15113	0.054489	0.006040
CRP, mg/l	0.075386	0.045461	0.20774	0.125274	0.098748
TNFα, pg/ml	0.071769	0.046442	0.23795	0.153976	0.123760

Table 8

Results of the multivariate linear regression analysis of the relationship between SYNTAX score and GDF-15 and endocan values

Parameter	β	Standard error β	*b*	Standard error *b*	*p*
Intercept	–	–	–2.35452	1.546611	0.129391
GDF-15, pg/ml	0.652809	0.051894	0.02430	0.001932	0.000000
ESM-1, ng/ml	0.154705	0.051894	0.17061	0.057228	0.003204

DISCUSSION

When studying cardiovascular risk factors, the relationship between atherosclerotic and inflammatory processes becomes obvious. A persistent increase in inflammation markers is closely associated with the development of adverse cardiovascular events caused by the rupture of atherosclerotic plaques [2].

It is necessary to note a significant number of studies examining the role of CRP and TNFα as representative laboratory markers for predicting major cardiovascular events [3]. Thus, more than twenty years ago, P.M. Ridker et al. showed that the inclusion of CRP and lipids is more effective in predicting the risk of MI compared to models using lipids only. Additionally, initial CRP levels predicted the risk of MI even in individuals with low total cholesterol or a high total cholesterol/high-density lipoproteins ratio [12]. In particular, the Reynolds scales were developed to estimate the risk of adverse cardiovascular events during a 10-year period in both women (Reynolds Risk Score) and men (Reynolds Risk Score for men), which included, among other things, the CRP level [13]. Of particular interest is a 2018 study involving 7,382 persons to confirm a new risk scoring system that incorporated factors such as CRP levels and quantification of calcium in the coronary arteries. This model, known as Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM), surpassed traditional scales, making it a potentially valuable tool for making risk-based decisions for the prevention of cardiovascular diseases [14].

In turn, it is well known that TNFα activates endothelial cells and induces the expression of cytokines and chemokines by monocytes/

macrophages, which lead to the progression of atherosclerotic processes. Apoptosis of endothelial cells plays an important role in the development of atherosclerosis [15]. TNFα induces apoptosis of endothelial cells by enhancing autophagy and promotes their premature aging [16]. It has been extensively studied that TNFα suppresses the regulation of the eNOS gene, leading to a decrease in the production of nitric oxide (NO) and, as a result, endothelial proliferation and inhibition of endothelium-dependent vasodilation [17].

A number of studies have demonstrated that TNFα causes endothelial dysfunction, promotes the formation of foam cells, angiogenesis, proliferation of smooth muscle cells, and thrombosis [18, 19].

However, there is growing interest in studying new laboratory markers of low-grade inflammation, such as GDF-15 and endocan. It is the ability of cardiomyocytes to produce GDF-15 in response to stress that underlies the diagnostic value of this marker. L. Lind et al. [20] studied the intima-media thickness and the plaque height in the carotid arteries using ultrasound and found that the proportion of thickened atherosclerotic plaques increased with the higher levels of GDF-15. A. Rohatgi et al. [21] demonstrated a positive correlation between GDF-15 and signs of subclinical coronary atherosclerosis and mortality. The data obtained in eight studies from an examination of 4,126 patients with heart failure demonstrated an association between excessive expression of GDF-15 and an increased risk of death [22]. Moreover, GDF-15 meets the criteria of R.S. Vasan (2006) as a biological marker of increased cardiovascular risk [23].

In turn, endocan expression in endothelial cells increases in response to inflammatory triggers such as lipopolysaccharides and cytokines (TNFα, transforming growth factor β1, fibroblast growth factor 2, interleukin-1β, hypoxia-inducible factor 1α), and decreases with interferon γ [24, 25]. Endocan also enhances the production of proinflammatory cytokines by endothelial cells, the expression of adhesion molecules, and the adhesion between monocytes and endothelial cells. In addition, endocan-activated adhesion molecules can secrete potent chemokines such as IL-8 and monocyte chemoattractant protein-1, which are necessary for the inflammatory response and contribute to the progression of atherosclerosis [26]. Several studies have investigated the role of endocan as a biomarker for predicting the severity of CHD using the Gensini and SYNTAX score, which take into consideration the anatomy, morphology, and severity of coronary artery stenosis and are widely used in clinical practice to choose the optimal type of treatment and predict overall cardiovascular risk. However, there have been conflicting results regarding the correlation of endocan with both scales, with some studies reporting significant, independent, and positive correlations [27, 28], while others did not find any significant associations [29, 30].

The present study has revealed higher concentrations of all low-grade inflammation markers in patients with CHD compared to the control group ($p < 0.0001$). There was also an increase in their values with the progression of the CA lesions ($p < 0.0001$). Statistically significant differences were found depending on the presence of such clinical signs as angina pectoris and a history of MI, as well as a number of correlations between their values and a number of clinical and instrumental characteristics. Subsequently, using the multivariate linear regression analysis, an attempt was made to assess the predictive significance of serum concentrations of CRP, TNFα, GDF-15, and ESM-1. The last two indicators demonstrated an independent relationship with the severity of atherosclerotic processes in the coronary bed. It should be noted, that GDF-15 turned out to be the most significant in this model ($\beta = 0.651$; $b = 0.026$; $p < 0.0001$).

CONCLUSION

The study demonstrated that simultaneous quantitative measurement of several laboratory parameters may be a more powerful tool for estimating the risk of coronary heart disease progression. This approach allows for a more accurate assessment of multiple aspects of pathogenesis. Furthermore, it was shown that endocan and, to a greater extent, GDF-15 are associated with the severity of atherosclerotic processes in the coronary arteries.

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Ushakov A.V. – literature analysis, data interpretation, study coordination, and final approval of the manuscript for publication. Zakharyan E.A. – conception and design, study coordination, obtaining and interpreting clinical data, drafting of the manuscript, and final approval of the manuscript for publication. Grigoriev P.E. – database compilation, statistical processing of study results, critical revision of the manuscript for important intellectual content, and final approval of the manuscript for publication. Malyi K.D. – literature analysis, obtaining and interpreting clinical data, and database compilation.

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