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The Role of Systemic Inflammatory Indices in Predicting Carotid Atherosclerosis in Patients with Rheumatoid Arthritis

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ABSTRACT

Aim. To determine the prognostic significance of systemic inflammatory indices for the development of carotid artery (CA) atherosclerosis in patients with rheumatoid arthritis (RA).

Materials and methods. A single-center, observational, cross-sectional study was conducted, which included 52 male and female patients with RA. The average age of the study participants was 59.5 ± 6.7 years. All patients underwent carotid duplex ultrasound. The intima – media thickness was recorded at ≥ 0.9 mm. A hemodynamically significant atherosclerotic plaque (AP) was considered to be a CA thickening of more than 50% compared to adjacent tissues. Based on the complete blood count data, the systemic inflammatory response index (SIRI), the aggregate index of systemic inflammation (AISI), the systemic immune – inflammation index (SII), the neutrophil-to-lymphocyte ratio (NLR), the lymphocyte-to-monocyte ratio (LMR), the platelet-to-lymphocyte ratio (PLR), and the Reis leukocyte index of intoxication were calculated. Binary logistic regression was used to develop a prognostic model.

Results. Based on the results of the carotid duplex ultrasound, the patients were divided into 2 groups: 32 patients (61.5%) with the presence of AP in the CA and 20 patients (38.5%) without AP. Patients with AP in the CA had higher values of NLR, SII, SIRI, and the Reis leukocyte index of intoxication. During the study, threshold values for these indices were determined, and a prognostic model for the probability of developing atherosclerosis of the CA in patients with RA was developed, in which the predictors were the values of the Reis index, SIRI, low-density lipoproteins, and age.

Conclusion. In RA, high activity of systemic inflammation is associated with the development of atherosclerotic arterial lesions, which should be taken into account when determining the tactics of managing these patients.

Keywords: rheumatoid arthritis, atherosclerosis, NLR, SIRI, SII, systemic inflammation

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Conformity with the principles of ethics. All patients signed informed consent to participate in the study. The study was approved by the local Ethics Committee of the National Ilizarov Medical Research Center for Traumatology and Orthopedics (Minutes No. 1 (76) dated November 29, 2024).

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Роль системных воспалительных индексов в прогнозировании атеросклероза сонных артерий у пациентов с ревматоидным артритом

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РЕЗЮМЕ

Цель. Определить прогностическую значимость системных воспалительных индексов для развития атеросклероза сонных артерий (СА) у пациентов с ревматоидным артритом (РА).

Материалы и методы. Проведено одноцентровое обсервационное кросс-секционное исследование, в которое были включены 52 пациента с РА. Средний возраст участников составил 59,5 ± 6,7 лет. Всем пациентам выполнено ультразвуковое дуплексное сканирование (УЗДС) СА. Утолщение комплекса интима-медиа фиксировали при значениях 0,9 мм и более. За гемодинамически значимую атеросклеротическую бляшку (АСБ) принимали утолщение СА свыше 50% в сравнении с близлежащими тканями. Проведен анализ наличия факторов риска сердечно-сосудистых заболеваний. На основании данных общего анализа крови рассчитывали индекс системного воспалительного ответа (SIRI), совокупный индекс системного воспаления (AISI), индекс системного воспаления (SII), нейтрофильно-лимфоцитарное соотношение (NLR), лимфоцито-моноцитарное соотношение (LMR), тромбоцитарно-лимфоцитарное соотношение (PLR), а также индекс Рейса. Для разработки прогностической модели использован метод бинарной логистической регрессии.

Результаты. По результатам УЗДС СА пациенты были разделены на две группы: 32 пациента (61,5%) с наличием АСБ в СА и 20 пациентов (38,5%) без АСБ. Пациенты с наличием АСБ в СА имели более высокие значения NLR, SII, SIRI, индекса Рейса. В ходе исследования определены пороговые значения для данных индексов, а также разработана прогностическая модель вероятности развития атеросклероза СА у пациентов с РА, в которой предикторами являлись значения индекса Рейса, SIRI, липопротеиды низкой плотности и возраст.

Заключение. При РА высокая активность системного воспаления ассоциирована с развитием атеросклеротического поражения артерий, что следует учитывать при разработке тактики ведения данных пациентов.

Ключевые слова: ревматоидный артрит, атеросклероз, NLR, SIRI, SII, системное воспаление

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

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

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом Национального медицинского исследовательского центра травматологии и ортопедии им. академика Г.А. Илизарова (протокол № 1 (76) от 29.11.2024).

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects joints and internal organs [1]. In 2020, there were over 17.6 million patients with RA worldwide, and the prevalence of the disease was 208.8 cases per 100,000 population, which is 14.1% more than in 1990. According to projections, by 2050, the global prevalence of RA will reach 31.7 million [2]. The prevalence of RA in the Russian Federation is 0.61% [3].

Patients with RA have an increased cardiovascular risk (CVR), which significantly contributes to overall cardiovascular mortality. This is primarily due to systemic inflammation, which is an independent factor in the development and progression of atherosclerosis. According to the World Health Organization, cardiovascular diseases (CVD) annually cause 17.9 million (32%) of all deaths worldwide [3]. Acute myocardial infarction (AMI) and stroke, which are most often caused by atherosclerosis, are the most significant causes of cardiovascular mortality [4].

The presence of atherosclerotic plaques (AP) in the carotid arteries (CA) is known to be a risk factor for ischemic stroke. According to the data of a systematic review and meta-analysis conducted by P. Ambrosino et al., patients with RA had higher values of the intima-media thickness (IMT) of the CA based on the results of carotid duplex ultrasound and also more often AP were detected in the CA (odds ratio (OR): 3.57; 95% confidence interval (95% CI): 1.69, 7.51; $p = 0.0008$) compared to the general population [5]. D.A. Galarza-Delgado et al. indicate that in RA, AP in the CA are formed more often than in the general population (30.0% versus 11.7%, $p = 0.013$), while bilateral AP are also detected significantly more often (8.3% versus 3.3%, $p = 0.008$) [6]. According to data from various studies in the Russian cohort, AP in the CA were detected in 59.5% (L.N. Eliseeva et al.) [7], 77% (O.A. Fomicheva et al.) [8], and 11% (E.V. Gerasimova et al.) of patients with RA [9].

The development and progression of atherosclerotic arterial lesions in RA are largely determined by the influence of systemic inflammation. Increased production of interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNFα) in RA induces the expression of adhesion molecules (vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin) on the surface of CA endothelial cells, which leads to a decrease in the production and bioavailability of nitric oxide (NO), an increase in the synthesis of endothelin-1, and hyperproduction of reactive oxygen species, contributing to increased oxidative stress and endothelial activation [10]. In addition, TNFα and IL-6 suppress the activity of lipoprotein lipase and lecithin cholesterol acyltransferase, which contributes to the formation of a proatherogenic lipid profile in RA, the development of oxidative modifications of low-density lipoproteins (LDL), and an increase in the production of dysfunctional high-density lipoproteins (HDL), leading to the progression of atherosclerotic lesions of the CA [11, 12]. Under conditions of systemic inflammation in RA, T-lymphocytes and monocytes are activated, which, under the influence of VCAM-1 and ICAM-1, migrate to the CA intima and infiltrate the AP, where they contribute to increased expression of proinflammatory cytokines and the development of AP instability [13].

The significant influence of inflammation on the development of carotid atherosclerosis and the contribution of the latter to the increase in CVR in patients with RA determine the special clinical significance of the search for predictors of this vascular lesion, which can be considered as systemic inflammatory indices based on the indicators of a complete blood count: the systemic inflammatory response index (SIRI), the aggregate index of systemic inflammation (AISI), the systemic immune – inflammation index (SII), the neutrophil-to-lymphocyte ratio (NLR), the lymphocyte-to-monocyte ratio (LMR), the platelet-to-lymphocyte ratio (PLR), the Reis leukocyte index of intoxication. Currently, the possibility of using systemic inflammatory indices in predicting atherosclerosis and CVR is being actively studied worldwide [14].

The aim of the study was to determine the prognostic significance of systemic inflammatory indices for the development of CA atherosclerosis in patients with RA.

MATERIALS AND METHODS

A single-center, observational, cross-sectional study was conducted, including 52 male and female patients (mean age 59.5 ± 6.7 years) with RA. Inclusion criteria were as follows: age from 35 to 75 years; RA diagnosis established in accordance

with the criteria of the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR). Patients meeting one of the following criteria were excluded from the study: coronary artery disease (CAD), chronic heart failure, acute or exacerbated chronic infection, cancer or history of cancer, and type 1 or type 2 diabetes mellitus. Patients underwent a general clinical examination in accordance with the 2024 Clinical Guidelines for Rheumatoid Arthritis of the Russian Association of Rheumatologists. All patients received basic anti-inflammatory therapy with one of the following medications: methotrexate, sulfasalazine, or leflunomide.

A carotid duplex ultrasound was performed for all patients by a single specialist – a functional diagnostics doctor – once during inpatient treatment in a specialized Rheumatology Unit. The carotid duplex ultrasound was performed using a Samsung RS85 ultrasound machine (South Korea). The linear transducer used in the study emitted a frequency of 7.5 MHz. The IMT of the CA was measured in mm at three points: the first point is the area of the general CA at a distance of 10 mm from the bulb; the second point is 5–10 mm cranial to the beginning of the bulb; the third point is the internal CA, 10 mm after the bifurcation on both sides. The maximum values of the IMT obtained during the study were analyzed. IMT was recorded at values of 0.9 mm or more. A hemodynamically significant AP was defined as a CA thickening over 50% compared to adjacent tissues [15, 16].

Total cholesterol (TC) was analyzed enzymatically, LDL and HDL were analyzed using a direct enzymatic colorimetric method, and triglycerides (TG) were analyzed using an enzymatic colorimetric method. A complete blood count was performed on a MINDRAY BC-6000 hematology analyzer (China). The erythrocyte sedimentation rate (ESR) was determined using the Westergren method. C-reactive protein (CRP) and IgM rheumatoid factor (RF) levels were analyzed using an immunoturbidimetric method on an ILab Taurus automated biochemical analyzer (USA). An enzyme-linked immunosorbent assay was used to determine the concentration of antibodies to cyclic citrullinated peptide (anti-CCP) in the serum.

Systemic inflammatory indices were calculated using the following formulas: SIRI = neutrophils x monocytes / lymphocytes [17]; AISI = neutrophils × monocytes × platelets / lymphocytes [18]; SII = neutrophils × platelets / lymphocytes [19]; NLR = neutrophils / lymphocytes [20]; PLR = platelets / lymphocytes [20]; LMR = lymphocytes / monocytes [21]; Reis index = (myelocytes + metamyelocytes + band neutrophils + segmented neutrophils) / (monocytes + lymphocytes + eosinophils) [22]. Absolute values of the number of formed elements in the blood were used for the calculation.

Microsoft Excel was used to create the study database. Statistical analysis was performed using STATISTICA 9 (StatSoft, USA). The normality of distribution of quantitative variables was assessed using the Shapiro – Wilk test, as well as analysis of the asymmetry and kurtosis coefficients. Data corresponding to a normal distribution were presented as the arithmetic mean (M) and standard deviation (SD). Indicators with a distribution different from the normal one were described using the median and interquartile range, Me [Q_1; Q_3]. Categorical variables were described as absolute values (n) and percentages (%).

Comparison of two independent groups for a quantitative indicator, the distribution of which in each of the groups corresponded to the normal one, under the condition of equal variances was performed using Student's t-test; in case of unequal variances, Welch's t-test was used. A comparison of two independent groups based on quantitative variables with non-normal distributions was performed using the non-parametric Mann – Whitney U-test. ROC analysis was used to assess the predictive value and discriminatory ability of quantitative variables for the target outcome. Classification quality was assessed based on the area under the ROC curve (AUC) with a 95% confidence interval. The cutoff value of the quantitative variable was determined by the highest value of the Youden's index. A predictive model for the probability of a specific outcome was constructed using logistic regression. Statistical significance of differences was determined at a significance level of $p < 0.05$.

RESULTS

Based on carotid duplex ultrasound data, all patients were divided into two groups: those with CA AP (n = 32; 61.5%) and those without them (n = 20; 38.5%). Patients in the study groups did not differ in

gender, age, disease duration and stage, CVD risk factors, or the proportion of patients receiving statins and glucocorticosteroids. No significant differences in lipid profile parameters were found between the patient groups. The presence of CA AP was statistically significantly more often associated with anti-CCP status and higher ESR and CRP values (Table 1). Systemic inflammation indices were higher in the presence of CA AP, while NLR, SII, SIRI, and Reis index values also differed statistically significantly (Table 2).

As a result of the ROC analysis conducted to assess the risk of the formation of AP in the CA, the threshold values of the studied indices of systemic inflammation were determined (Table 3, Figure).

Table 1

Comparative Characteristics of Patients with and without Carotid Artery Atherosclerosis

Indicator	Patients with the presence of AP in the carotid arteries (n = 32)	Patients without AP in the carotid arteries (n = 20)	p
Age, years, $M \pm SD$	60.4±6.5	58.6±7.1	0.06
Gender (male), n (%)	9 (28.1)	6 (30)	0.07
Duration of disease, years, Me [Q_1; Q_3]	11.9 [7.4; 14.3]	10.8 [6.1; 13.9]	0.21
Disease stage, early/advanced/late, n (%)	5 (15.6) / 11 (34.4) / 16 (50)	3 (15) / 3 (15) / 14 (70)	0.19
Positive RF, n (%)	25 (78.1)	16 (80)	0.44
Positive anti-CCP, n (%)	23 (71.8)	13 (65)	0.03
Hypertension, n (%)	14 (43.8)	8 (40)	0.29
Statin therapy, n (%) Atorvastatin, n (%) Average dose, mg, $M \pm SD$ Rosuvastatin, n (%) Average dose, mg, $M \pm SD$	15 (46.9) 8 (25) 26.25±8.5 7 (21.9) 10.7±3.5	9 (45) 6 (30) 20±6.5 3 (15) 13.3±4.2	0.36 0.08 0.25 0.07 0.23
Glucocorticosteroid therapy, n (%)	6 (18.8)	3 (15)	0.22
Smoking, n (%)	7 (21.8)	4 (20)	0.17
Family history of CVD, n (%)	6 (18.8)	5 (25)	0.06
Antirheumatic therapy: Methotrexate Leflunomide Sulfasalazine, n (%)	 15 (46.8) 8 (25) 9 (28.2)	 9 (45) 6 (30) 5 (25)	 0.54 0.19 0.12
TC, mmol/l, $M \pm SD$	5.21±1.22	5.03±0.98	0.11
LDL, mmol/l, Me [Q_1; Q_3]	3.31 [2.2; 3.98]	3.12 [2.11; 3.77]	0.09
HDL, mmol/l, Me [Q_1; Q_3]	0.89 [0.68; 1.01]	0.78 [0.65; 0.99]	0.078
TG, mmol/l, $M \pm SD$	1.77±0.33	1.71±0.41	0.15
ESR, mm/h, Me [Q_1; Q_3]	27 [22; 31]	20 [16; 25]	0.03
CRP, mg/l, $M \pm SD$	6.28±1.17	3.22±1.12	0.02

Note. AP – atherosclerotic plaque; RF – rheumatoid factor; anti-CCP – antibodies to cyclic citrullinated peptide; CVD – cardiovascular disease; TC – total cholesterol; LDL – low-density lipoprotein; HDL – high-density lipoprotein; TG – triglycerides; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; p – level of statistical significance of differences.

Table 2

Values of Systemic Inflammation Indices in Patients with and without Carotid Artery Atherosclerosis, Me [Q_1; Q_3]

Index	Patients with the presence of AP in the carotid arteries (n = 32)	Patients without AP in the carotid arteries (n = 20)	p
NLR	2.31 [1.72; 3.59]	1.48 [1.21; 2.21]	0.01
LMR	4.78 [2.9; 6.1]	4.01 [2.76; 5.8]	0.17
PLR	178.9 [129.7; 213.24]	159 [109.3; 179.9]	0.29
Reis index	1.64 [1.21; 2.11]	1.26 [1.11; 1.43]	0.002
SII	794.2 [440.5; 1,090.8]	411.11 [360.06; 582.93]	0.004
SIRI	1.35 [0.77; 1.57]	0.74 [0.53; 0.89]	0.01
AISI	255.3 [199.1; 279.2]	219.8 [165; 231.5]	0.059

Note. AP – atherosclerotic plaque; LMR – lymphocyte-monocyte ratio; PLR – platelet-lymphocyte ratio; NLR – neutrophil-lymphocyte ratio; SII – systemic immune-inflammation index; SIRI – systemic inflammatory response index; AISI – aggregate inflammation systemic index; p – level of statistical significance of differences.

Table 3

Results of ROC Analysis for Determining Threshold Values of Systemic Inflammatory Indices Associated with the Presence of AP in the CA

Index	Threshold value	AUC	95% CI for AUC	*p*
NLR	>1.756	0.754	0.583–0.926	0.029
SII	>585.29	0.751	0.577–0.926	0.021
SIRI	>1.04	0.768	0.599–0.937	0.022
AISI	>247.4	0.699	0.577–0.874	0.032
Reys index	>1.57	0.791	0.698–0.897	0.007

Note. AUC – area under the curve.

As a result of the analysis conducted using binary logistic regression, a prognostic model was developed for assessing the risk of AP formation in the CA in patients with RA. The model includes a set of independent predictors statistically significantly associated with the outcome under study (the presence of AP in the CA in patients with RA) and allows for calculating the personalized probability of this complication.

The observed dependence was described by the equation: $P = 1 / (1 + e^{-z})$; $z = -4.710 + 1.374 \times$ (Reis index) + $0.745 \times$ (SIRI) − $0.331 \times$ (LDL) + $0.057 \times$ (age), where P is the risk assessment of AP formation in the CA in patients with RA, and *z* is the value of the logistic function. The discriminatory ability of the regression model was assessed using ROC analysis, during which the threshold P value was defined as 0.615. The probability of the presence of AP in the CA in patients with RA was predicted by a P value greater than or equal to this value. The sensitivity and specificity of the developed model were 78.9% and 81.8%, respectively.

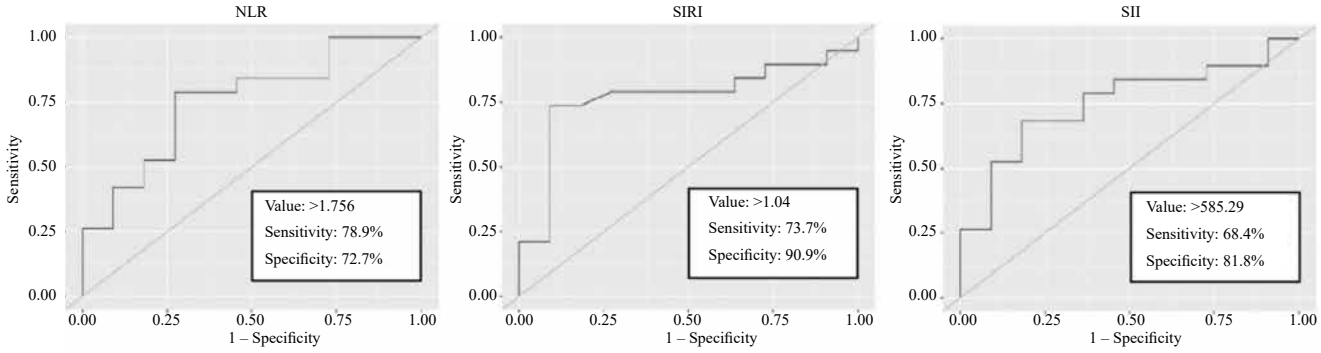

Figure. ROC curve characteristics of the threshold values of systemic inflammatory indices (NLR, SIRI, and SII) for optimal binary classification of the presence or absence of carotid artery atherosclerosis in patients with rheumatoid arthritis. ROC analysis: NLR – neutrophil-to-lymphocyte ratio, SIRI – systemic inflammatory response index, SII – systemic immune-inflammation index. The ordinate axis shows sensitivity (%), the abscissa axis – 1 minus specificity (%). The rectangles show sensitivity and specificity estimates, as well as the threshold values of the systemic inflammatory indices

DISCUSSION

Data from cohort studies indicate an association between peripheral blood leukocyte levels and their major subpopulations (neutrophils, lymphocytes, and monocytes) and an increased risk of stroke, CAD, and all-cause mortality. The simplicity and accessibility of this analysis have facilitated the active study of calculated leukocyte indices (LMR, NLR, and PLR) as markers of systemic inflammation. Numerous studies confirm that these indices have a higher predictive power for overall and cardiovascular mortality compared to the use of absolute leukocyte count alone [23].

Systemic inflammatory indices (SII, SIRI, and AISI) are expanded versions of indices calculated based on leukocyte differential parameters. Although the importance of systemic inflammatory indices for predicting the course and outcome of various diseases has only recently been studied, and the accumulated scientific data are still insufficient, a number of publications indicate their potential clinical significance in oncological, infectious, autoimmune, and cardiovascular pathologies [24].

Y. Xia et al. found that patients with SII >655.56 had significantly higher rates of overall mortality (OR = 1.29; 95% CI): 1.18–1.41) and CVD mortality (OR = 1.33; 95% CI: 1.11–1.59) compared to the SII group (<335.36). Similarly, the risk of all-cause (OR = 1.39; 95% CI: 1.26–1.52) and CVD mortality (OR = 1.39; 95% CI: 1.14–1.68) was increased in the group with SIRI >1.43 relative to the group with SIRI <0.68 [25].

Of particular interest are the data of V.A. Schwartz et al., who found that in patients without RA, the threshold levels of systemic inflammatory indices associated with atherosclerosis were equal for NLR >2.05, for SIRI >1.05, and for SII >368 [26]. E. Zhou et al. found that in patients with RA with an NLR value >3.28, the risk of death from all causes (relative risk (RR) = 2.02, 95% CI: 1.53–2.66) and from cardiovascular pathology (RR = 2.48, 95% CI: 1.34–4.57) was higher than in patients with a lower value of this index [27]. According to X. Yin et al., in RA, a higher SII level was associated with a 1.48-fold increase in the risk of all-cause mortality (RR = 1.48, 95% CI: 1.21–1.81) and a 1.51-fold increase in the risk of cardiovascular mortality (RR = 1.51, 95% CI: 1.04–2.18) compared to lower SII [28]. The SIRI inflammatory index also demonstrated a positive correlation with all-cause and CVD mortality in patients with RA [29]. According to M. González-Sierra et al., in patients with RA, the values of the SIRI, NLR, and PLR indices were not associated with CA atherosclerosis, but they had a positive correlation with the CVR assessed by the SCORE2 scale [30].

According to our data, the threshold values that were statistically significantly associated with the presence of AP in the CA in patients with RA were: for SII >585.29; for SIRI >1.04; for NLR >1.756; and for AISI >247.4. The increase in the values of systemic inflammation indices is due to characteristic changes in the leukocyte formula and platelet component: an increase in the absolute number of neutrophils, monocytes and platelets against the background of a decrease in the number of lymphocytes. In RA, high levels of TNFα, IL-1, and IL-6 stimulate the production of neutrophils, and increased concentrations of chemokines (CXCL1, CXCL2, CXCL5, etc.) secreted by synovial fibroblasts, macrophages, and other cells at the site of inflammation cause the migration of neutrophils from the bloodstream into the synovial membrane and other tissues, which is accompanied by a compensatory increase in the production of neutrophils by the bone marrow [31].

IL-6 plays a central role in the pathogenesis of reactive thrombocytosis in RA: it induces increased synthesis of thrombopoietin, a key hormonal regulator of thrombopoiesis in hepatocytes, and simultaneously has a direct stimulating effect on megakaryocytic progenitor cells and mature megakaryocytes in the bone marrow, activating the JAK/STAT (janus kinase/signal transducer and activator of transcription proteins) and MAPK (mitogen-activated protein kinase) signaling pathways, which leads to increased proliferation, accelerated differentiation, increased ploidy of megakaryocytes, and, as a consequence, increased platelet release [32]. Increased platelet counts and activation are considered as factors potentially contributing to increased CVR and persistent inflammation in the vascular bed, as well as in the synovial lining of joints in RA.

Lymphocytopenia in patients with RA is a common hematological manifestation reflecting profound immune dysregulation and having a multifactorial nature. Key proinflammatory cytokines (TNFα, IL-6, etc.) enhance the expression of the Fas receptor (CD95) on lymphocytes and increase the level of soluble Fas ligand (sFasL), triggering the caspase cascade and activation-induced cell death [33]. Hypoxia and the Warburg effect in the synovium cause competition for glucose and the accumulation of lactate, which suppresses lymphocyte function and induces their apoptosis by disrupting the PI3K/Akt/mTOR (Phosphoinositide 3-kinases/Protein kinase B/mammalian target of rapamycin) survival signaling pathways.

In addition, the presence of antilymphocyte autoantibodies and increased expression of inhibitory receptors (PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4) on chronically activated T cells lead to their lysis, opsonization, or a state of functional exhaustion with an increased tendency to apoptosis [33]. Limitations of the present study included its single-center and cross-sectional nature, as well as a small sample size of patients.

CONCLUSION

This study demonstrates that in patients with RA, elevated systemic inflammatory indices are significantly associated with the presence and severity of atherosclerosis. These indices, easily calculated using routine clinical blood tests, reflect the intensity and imbalance of the systemic immune inflammatory process underlying RA, making them accessible, noninvasive, and cost-effective biomarkers of elevated CVR in patients with RA.

Monitoring systemic inflammatory indices can complement traditional CVR assessment scales (SCORE, SCORE2, etc.) and facilitate the early identification of patients requiring more intensive preventive strategies. Persistently elevated values of these indices may indirectly indicate a more aggressive course of RA with a pronounced systemic inflammatory component directly damaging the vascular wall.

Determining optimal cutoff values for each index in patients with RA and assessing their additional diagnostic and prognostic value compared to existing markers (CRP, ESR) and assessment tools (carotid duplex ultrasound and coronary artery calcium levels) are a pressing scientific challenge. Randomized controlled trials are needed to establish a causal relationship and determine the prognostic value of changes in systemic inflammatory indices in relation to atherosclerosis progression and the occurrence of cardiovascular events (myocardial infarction, stroke) in patients with RA.

Of equal importance is the study of how various RA treatment strategies (especially therapy with biological disease-modifying antirheumatic drugs and targeted synthetic disease-modifying antirheumatic drugs) influence the changes in systemic inflammatory indices and, consequently, the risk of atherosclerosis and cardiovascular events. The development and validation of clinically applicable algorithms integrating these indices into routine CVR assessment and preventive therapy decision-making in patients with RA is of significant scientific interest.

REFERENCES

1. Lyubimova L.V., Pchelova N.N., Nikolaev N.S., Preobrazhenskaya E.V., Lyubimov E.A. Periprosthetic Joint Infection in Patients with Rheumatoid Arthritis: Case Series. *Genij Ortopedii*. 2024;30(4):552–560. (In Russ.). DOI: 10.18019/1028-4427-2024-30-4-552-560.
2. Black R.J., Cross M., Haile L.M., Culbreth G.T., Steinmetz J.D., Hagins H. et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol.* 2023;5:e594–e610. DOI: 10.1016/s2665-9913(23)00211-4.
3. Galushko E.A., Nasonov E.L. Prevalence of Rheumatic Diseases in Russia. *Almanac of Clinical Medicine*. 2018;46(1):32–39. (In Russ.). DOI: 10.18786/2072-0505-2018-46-1-32-39.
4. Roth G.A., Abate D., Abate K.H., Abay S.M., Abbafati C., Abbasi N. et al. Global Health Metrics. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* 2018;392(10159):1736–1788. DOI: 10.1016/S0140-6736(18)32203-7.
5. Ambrosino P., Lupoli R., Di Minno A., Tasso M., Peluso R., Di Minno M.N. Subclinical atherosclerosis in patients with rheumatoid arthritis. A meta-analysis of literature studies. *Thromb. Haemost.* 2015;113(5):916–30. DOI: 10.1160/TH14-11-0921.
6. Galarza-Delgado D.A., Azpiri-Lopez J.R., Guajardo-Jauregui N., Cardenas-de la Garza J.A., Garza-Cisneros A.N., Garcia-Heredia A. et al. Carotid atherosclerosis in the first five years since rheumatoid arthritis diagnosis: a cross sectional study. *Adv. Rheumatol.* 2023;63(1):36. DOI: 10.1186/s42358-023-00319-x.
7. Eliseeva L.N., Otarova Zh.Z., Zhdamarova O.I., Davydova A.F. Clinical Efficacy of a Method for Identifying Patients at High Risk of Carotid Atherosclerosis in Rheumatoid Arthritis. *South Russian Journal of Therapeutic Practice*. 2022;3(4):70–76. (In Russ.). DOI: 10.21886/2712-8156-2022-3-4-70-76.
8. Fomicheva O.A., Popkova T.V., Krugly L.B., Gerasimova E.V., Novikova D.S., Pogorelova O.A. et al. Factors of Progression and Occurrence of Atherosclerosis in Rheumatoid Arthritis. *Kardiologiia*. 2021;61(1):12–21. (In Russ.). DOI: 10.18087/cardio.2021.1.n1331.
9. Gerasimova E.V., Popkova T.V., Shalygina M.V., Kirillova I.G., Gerasimova D.A., Glukhova S.I. et al. Subclinical Atherosclerosis of the Carotid Arteries in Patients with Rheumatoid Arthritis with Low Cardiovascular Risk. *Terapevticheskii Arkhiv*. 2023;95(5):375–379. (In Russ.). DOI: 10.26442/00403660.2023.05.202203.
10. England B.R., Thiele G.M., Anderson D.R., Mikuls T.R. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ.* 2018;361:k1036. DOI: 10.1136/bmj.k1036.
11. Feingold K.R., Grunfeld C. Effect of inflammation on HDL structure and function. *Curr. Opin. Lipidol.* 2016;27(5):521–530. DOI: 10.1097/MOL.0000000000000333.
12. Chang C.K., Chiang E.I., Chang K.H., Tang K.T., Chen P.K., Yip H.T. et al. The sizes and composition of HDL-cholesterol are significantly associated with inflammation in rheumatoid arthritis patients. *Int. J. Mol. Sci.* 2023;24(13):10645. DOI: 10.3390/ijms241310645.
13. Certo M., Rahimzadeh M., Mauro C. Immunometabolism in atherosclerosis: a new understanding of an old disease. *Trends. Biochem. Sci.* 2024;49(9):791–803. DOI: 10.1016/j.tibs.2024.06.003.
14. Jin Z., Wu Q., Chen S., Gao J., Li X., Zhang X. et al. The Associations of Two Novel Inflammation Indexes, SII and SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: A Ten-Year Follow-Up Study in 85,154 Individuals. *J. Inflamm. Res.* 2021; 14:131–40. DOI:10.2147/JIR.S283835.
15. Johri A.M., Nambi V., Naqvi T.Z., Feinstein S.B., Kim E.SH., Park M.M. et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. *J. Am. Soc. Echocardiogr.* 2020;33(8):917–933. DOI: 10.1016/j.echo.2020.04.021.

16. Chernyavsky M.A., Irtyuga O.B., Yanishevsky S.N., Alieva A.S., Samochernykh K.A., Abramov K.B. et al. Russian Consensus Statement on the Diagnosis and Treatment of Patients with Carotid Stenosis. *Russian Journal of Cardiology*. 2022;27(11):5284. (In Russ.). DOI: 10.15829/1560- 4071-2022-5284.
17. Qi Q., Zhuang L., Shen Y., Geng Y., Yu S., Chen H. et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer.* 2016;122(14):2158–67. DOI: 10.1002/cncr.30057.
18. Xiu J., Lin X., Chen Q., Yu P., Lu J., Yang Y. et al. The aggregate index of systemic inflammation (AISI): a novel predictor for hypertension. *Front. Cardiovasc. Med.* 2023;10:1163900. DOI: 10.3389/fcvm.2023.1163900.
19. Hu B., Yang X.R., Xu Y., Sun Y.F., Sun C., Guo W. et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin. Cancer. Res.* 2014;20(23):6212–22. DOI: 10.1158/1078-0432.CCR-14-0442.
20. Diem S., Schmid S., Krapf M., Flatz L., Born D., Jochum W. et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer.* 2017;111:176–181. DOI: 10.1016/j.lungcan.2017.07.024.
21. Abe S., Kawai K., Nozawa H., Hata K., Kiyomatsu T., Morikawa T. et al. LMR predicts outcome in patients after preoperative chemoradiotherapy for stage II-III rectal cancer. *J. Surg. Res.* 2018;222:122–131. DOI: 10.1016/j.jss.2017.09.053.
22. Grebennikova I.V., Lidokhova O.V., Makeeva A.V., Bolotrskikh V.I., Berdnikov A.A., Savchenko A.P. et al. Clinical and Pathogenetic Significance of Leukocyte Indices in COVID-19: a Restrospective Study. *Bashkortostan Medical Journal.* 2022;17(3):10–14. (In Russ.).
23. Joshi A., Bhambhani A., Barure R., Gonuguntla S., Sarathi V., Attia A.M. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as markers of stable ischemic heart disease in diabetic patients: An observational study. *Medicine.* 2023;102(5):e32735. DOI: 10.1097/MD.0000000000032735.
24. Cheng Q., Liu C., Zhong H., Wang Z., Zhou S., Sun J. et al. Comparison of systemic immunoinflammatory biomarkers for assessing severe abdominal aortic calcification among US adults aged ≥40 years: A cross-sectional analysis from NHANES. *PLoS One*. 2025;20(6):e0325949. DOI: 10.1371/journal.pone.0325949.
25. Xia Y., Xia C., Wu L., Li Z., Li H., Zhang J. Systemic Immune Inflammation Index (SII), System Inflammation Response Index (SIRI) and Risk of All-Cause Mortality and Cardiovascular Mortality: A 20-Year Follow-Up Cohort Study of 42,875 US Adults. *J. Clin. Med.* 2023;12(3):1128. DOI: 10.3390/jcm12031128.
26. Schwartz V.A., Talibova S.M., Sokolskaya M.A, Ispiryan A.Yu., Shvarts E.N., Petrosyan A.D. et al. Association of Novel Biomarkers of Systemic Inflammation with Atherosclerosis and its Severity. *Russian Journal of Cardiology*. 2024;29(8):6025. (In Russ.). DOI: 10.15829/1560-4071-2024-6025.
27. Zhou E., Wu J., Zhou X., Yin Y. The neutrophil-lymphocyte ratio predicts all-cause and cardiovascular mortality among U.S. adults with rheumatoid arthritis: results from NHANES 1999–2020. *Front. Immunol.* 2023;14:1309835. DOI: 10.3389/fimmu.2023.1309835.
28. Yin X., Zhang Y., Zou J., Yang J. Association of the systemic immune-inflammation index with all-cause and cardiovascular mortality in individuals with rheumatoid arthritis. *Sci. Rep.* 2024;14(1):15129. DOI: 10.1038/s41598-024-66152-4.
29. Wang W., Yao W., Tang W., Li Y., Lv Q., Ding W. Systemic inflammation response index is associated with increased all-cause and cardiovascular mortality in US adults with rheumatoid arthritis. *Prev. Med.* 2024;185:108055. DOI: 10.1016/j.ypmed.2024.108055.
30. González-Sierra M., Quevedo-Rodríguez A., Romo-Cordero A., González-Chretien G., Quevedo-Abeledo J.C., de Vera-González A. et al. Relationship of blood inflammatory composite markers with cardiovascular risk factors and subclinical atherosclerosis in patients with rheumatoid arthritis. *Life (Basel).* 2023;13(7):1469. DOI: 10.3390/life13071469.
31. Karmakar U., Vermeren S. Crosstalk between B cells and neutrophils in rheumatoid arthritis. *Immunology*. 2021;164(4):689–700. DOI: 10.1111/imm.13412.
32. Harifi G., Sibilia J. Pathogenic role of platelets in rheumatoid arthritis and systemic autoimmune diseases. Perspectives and therapeutic aspects. *Saudi Med. J.* 2016;37(4):354–60. DOI: 10.15537/smj.2016.4.14768.
33. Wang Y., Su R., Li B., Guo Q., Hu F., Yu X. et al. Reduction of peripheral regulatory T cells in active rheumatoid arthritis patients with coronary artery disease. *BMC Immunol.* 2021;22(1):76. DOI: 10.1186/s12865-021-00466-0.

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