

Analysis of peripheral blood parameters for the diagnosis of inflammatory activity in rheumatoid arthritis

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Summary

Background: Currently, it is considered generally accepted to assess the activity of inflammation in rheumatoid arthritis (RA) according to the disease activity index (DAS28), which requires computer technology. However, there have been reports that inflammatory activity in autoimmune diseases can be diagnosed with peripheral blood counts.

Purpose: To clarify the possibility of using peripheral blood parameters for the diagnosis of inflammatory activity in RA.

Material and methods: The study included 100 patients with RA who were consecutively hospitalized in the first quarter of 2021 due to an exacerbation. The control group consisted of 59 healthy donors. When patients were admitted to the clinic, along with standard clinical, laboratory and radiological parameters, the neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios were determined.

Results: Correlation analysis of the studied clinical and laboratory parameters of the inflammatory activity of RA patients using the Pearson method showed that the NLR indicator, in contrast to the PLR, was statistically significant ($p < 0.05$) correlated with the number of swollen joints (SJC) $r = 0.236$, the values of C-reactive protein (CRP) $r = 0.448$, DAS28ESR $r = 0.274$, erythrocyte sedimentation rate (ESR) ($r = 0.274$). ROK-analysis of the sensitivity and specificity of the NLR value in relation to the CRP and ESR indicators confirmed an acceptable level of sensitivity and specificity in assessing the inflammatory activity of RA.

Conclusions: The NLR index, calculated from the data of the analysis of peripheral blood, can be used in clinical practice as an objective and accessible marker of the inflammatory activity of RA.

Keywords: Rheumatoid arthritis; assessment of inflammatory activity; DAS28ESR, NLR; PLR.

Introduction

RA is an autoimmune disease manifested primarily by inflammation of the synovial joints (synovitis), followed by their deformation and loss of function, which seriously affects the quality of life [1]. According to the classification criteria ACR / EULAR (2010), visually confirmed synovitis is the main sign of RA [2]. Therefore, its dynamics, reflecting the activity of inflammation, is a key indicator of the effectiveness of RA treatment. The worldwide accepted principle of RA treatment is "treatment to target" (T2T), which has been defined as clinical remission or at least low disease activity [3, 4]. To assess RA activity, the Disease Activity Score with 28-joint counts (DAS-

28ESR), approved in 2007 at a meeting of the Plenum of the Board of the All-Russian public organization "Association of Rheumatologists of Russia", is now widely used [5, 6]. At the same time, inflammatory activity can be diagnosed with the results of a general blood test because the indicators of the ratio of neutrophils to lymphocytes (NLR) and platelets to lymphocytes (PLR) are markers of inflammation in autoimmune diseases [7-9], and in particular in rheumatoid arthritis [10, 11]. In the Russian population of RA patients, no such studies have been carried out.

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Purpose

To clarify the possibility of using peripheral blood parameters for the diagnosis of inflammatory activity of RA.

Table 1: Clinical characteristics and laboratory parameters of patients with RA.

Indicator	Values
Gender (women / men),n(%)	83(83 %)/17(17%)
Age, years (M±σ)	53,5±12,4
Age of disease onset, years (M±σ)	41,4±13,8
Duration of illness, years, Me [25th; 75th percentile]	10[3; 16]
Presence of rheumatoid factor, n (%)	89(89)
The presence of antibodies to cyclic citrullinated peptide, n (%)	78(78)
Clinical stage, n (%)	
Deployed	70(70)
Late	30(30)
The number of painful joints (TJC) of 28 joints, (M±σ)	10,0±6,1
Number of swollen joints (SJC) of 28 joints , (M±σ)	6,4±5,0
DAS28 _{ESR} (M±σ)	5,4±1,4
X-ray stage, n (%)	
I	2(2)
II	54(54)
III	24(24)
IV	20(20)
Functional class, n (%)	
I	2(2)
II	81(81)
III	15(15)
IV	2(2)
ESR according to Westergren, mm / hour (M±σ)	35,7+33,6
CRP, mg/l (M±σ)	23,0+30,3
NLR (M±σ)	2,4+1,5
PLR (M±σ)	181,3+83,4

Material and Methods

The study included 100 patients with RA (meeting the classification criteria ACR / EULAR 2010 [11], consistently hospitalized from different regions of Russia in the first quarter of 2021, to receive high-tech medical care in connection with an exacerbation. The control group consisted of 59 healthy donors (23 women and 36 men), whose average age was 31.6 ± 7.2 years: NLR indices - 1.61 ± 0.47 (NLR values no more than 2.3 are considered normal); PLR - 116.78 ± 36.59 (the norm is considered to be a PLR value of not more than 168). When patients were admitted to the clinic, along with standard clinical laboratory and radiological parameters, NLR and PLR indices were determined. To analyze the data obtained, we used the Microsoft Excel application and the Statistica 10 for Windows statistical data analysis package (StatSoft Inc., USA). Quantitative variables were described by the following statistical characteristics: the number of patients, the arithmetic mean (M), the standard deviation from the arithmetic mean (σ), the 25th

and 75th percentiles, and the median. Qualitative variables were described by absolute and relative frequencies (percentages). Differences were considered statistically significant at the achieved level of statistical significance p <0.05. For quantitative variables, a test for compliance with the normal distribution law was performed. The evaluation of the obtained results of the study was carried out using methods of statistical analysis - nonparametric Mann-Whitney tests and Wilcoxon's test. In order to determine the sensitivity and specificity of the new indices of RA activity, an ROK-analysis was performed in relation to the activity of the disease, determined by the known DAS28ESR index.

Results

The clinical characteristics and laboratory parameters of the RA patients included in the study are presented in (Table 1).

Table 2 shows the data of the correlation analysis of NLRs with the studied clinical and laboratory parameters of inflammation in patients with RA.

Table 2: Correlation analysis of NLRs with the studied clinical and laboratory parameters of inflammation in RA patients using the Pearson method.

Indicators	NLR	PLR
TJC(of 28 joints)	.1569	.0469
	p=.117	p=.642
SJC (of 28 joints)	.2363	.0846
	p=.018	p=.403
*PtGA(100 mm VAS)	.0854	-.0759
	p=.398	p=.453
ESR,mm/hour	.2738	.1589
	p=.005	p=.111
CRP mg/l)	.4484	.1622
	p=.000	p=.107
DAS28 _{ESR}	.2830	.1414
	p=.004	p=.156

*PtGA is a general assessment of the state of health of patients on a 100 mm visual analogue scale (VAS).

It follows from the table that the level of NLR, in contrast to PLR, statistically significantly (p <0.05) correlated with the values of SJC (r = 0.236), CRP (r = 0.448), DAS28ESR (r = 0.274), ESR (r = 0.274), but did not correlate with TJC (r = 0.156) and PtGA (r = 0.085).

According to the data of correlation analysis according to Spearman's method, the level of NLR > N statistically significantly (p <0.05) correlated with the indicators of inflammation: SJC (r = 0.266), TJC (r = 0.214), CRP (r = 0.483), DAS-28ESR (r = 0.267), ESR (r = 0.329).

Figure 1.2 shows the scatter diagrams of the correlation analysis of NLR and CRP; NLR and DAS28ESR, respectively.

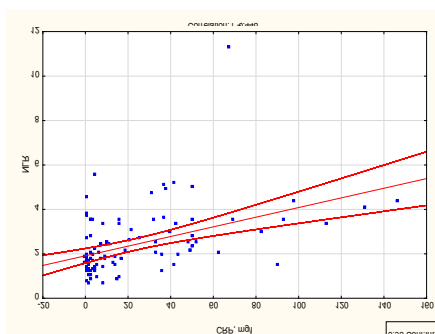


Figure 1: Correlation analysis of NLR and CRP. Scatter plot.

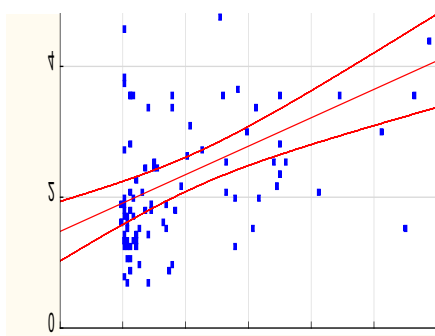


Figure 2: Correlation analysis of NLR and DAS28ESR. Scatter plot.

Table 3 shows the NLR values depending on the CRP index in RA patients.

Table 3: NLR values in RA patients depending on the CRP index.

Laboratory indicator	NLR Me (25th-75th percentile)	NLR (10th-90th percentile)	p, criterion Mann-Whitney
*CRP ≤ 5 mg/l (n=40) CRP > 5 mg/l (n=60)	1,6 (1,3-2,0) 2,4 (1,8-3,4)	1-3,54 1,3-4,5	0,001

*CRP ≤ 5 mg/l – normal values.

In the control group, the NLR indicator varied within 1.61 ± 0.47.

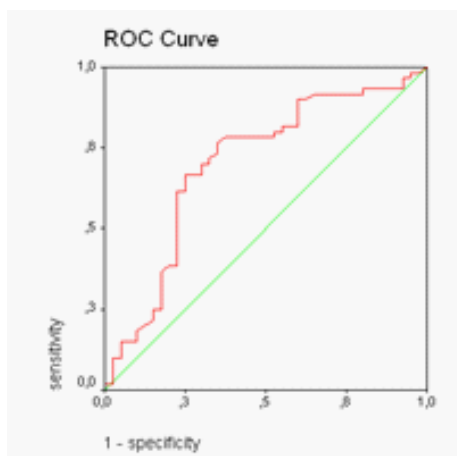


Figure 3: ROK-analysis of the sensitivity and specificity of the NLR value in relation to the CRP indicator.

The figure shows that the area under the curve was 0.701 (0.591-0.81), p < 0.001. With NLR values equal to 2.1, the sensitivity was 60%, the specificity was 77%, which shows the correspondence of increased NLR values to higher CRP values.

Table 4 shows the NLR values depending on the ESR index in RA patients.

Table 4: NLR values in RA patients depending on ESR index.

Laboratory indicators	NLR Me (25th-75th percentile)	NLR Me (10th-90th percentile)	p, criterion Mann-Whitney
*ESR ≤ N mg/l (n=58) ESR > N mg/l (n=42)	1,7 (1,31-2,38) 2,52 (1,9-3,54)	1,17-3,54 1,23-4,71	0,001

*ESR ≤ 15 (men under 50), ESR ≤ 20 (women under 50), ESR ≤ 20 (men over 50), ESR ≤ 30 (women over 50) mm/hour – normal values.

ROK-analysis of the NLR index in relation to the increased level of ESR (> N) also confirmed a good level of sensitivity and specificity of the test under study (Figure 4).

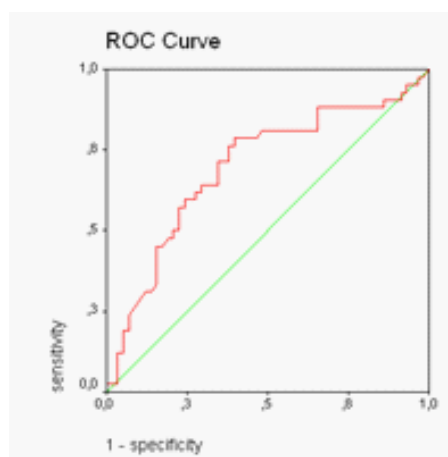


Figure 4: ROK-analysis of the sensitivity and specificity of the NLR value in relation to the ESR indicator.

The figure shows that the area under the curve was 0.695 (0.587-0.803), p < 0.001. With NLR values equal to 2.1, the sensitivity was 64%, the specificity was 69%.

Discussion

Neutrophils, lymphocytes, and platelets play an important role in the control of inflammation in RA, and their determination in peripheral blood has begun to be used as surrogate indicators. It is believed that neutrophils are key participants in the pathogenesis of RA, promoting the activation of antigen-presenting cells, the production of prooxidant mediators and lytic enzymes in the microenvironment of the joints [12, 13]. More recently, the release of neutrophilic extracellular traps containing a large amount of citrullinated proteins by neutrophils from RA patients has been attributed to the decisive role in the dysregulation of the adaptive response of the immune system [14, 15]. The role of platelets in the pathogenesis of RA seems to be more controversial [16]. However, NLRs and PLRs, which are easy to determine by doing a complete blood count, may reflect the progression and activity of the disease. This aspect is potentially relevant because, despite the increase in information about interleukins, cytokines, and serum autoantibodies in RA, there remains a need to identify better diagnostic markers of systemic inflammation than traditional CRP and ESR. Therefore, two meta-analyses are devoted to the study of the value of NLR and PLR indicators in RA [9, 10]. In the first, three studies were analyzed and it was found that in patients with RA, the NLR and PLR indices are noticeably higher than in healthy people in the control group. Therefore, the authors concluded that NLR and PLR indices can be recommended as

diagnostic markers of inflammation in RA [9]. In the second meta-analysis, which covered 13 studies, the NLR rate was assessed in 1550 RA patients (477 men and 1073 women) and 1128 healthy patients (326 men and 802 women). The mean age of patients and healthy people was $52,1 \pm 2,4$ and $47,1 \pm 1,7$ years respectively.

CRP and ESR indices in RA patients ranged from 1.1 to 38.6 mg / l and from 16.8 to 108.41 mm / h, respectively, indicating a high variability of inflammation. In RA patients, high NLR indices were observed in comparison with controls [10].

Our study on the Russian population of RA patients showed the possibility of diagnosing inflammatory activity based on the result of a general blood test, by assessing the neutrophil-to-lymphocyte ratio (NLR). Characteristic features of the NLR used:

- Acceptable measures of sensitivity and specificity.
- Easy to count.
- No special equipment and additional costs are required.
- Available for widespread use in clinical practice.
- Convenient for routine monitoring of inflammatory activity in rheumatoid arthritis.
- Statistically significant correlates with the values of SJC, CRP, DAS28ESR and ESR.
- Can be determined in absentia, without limiting the number of patients.

At the same time, the RA activity indicator recommended in Russia is calculated by the formula $DAS28\ ESR = 0.56 \sqrt{TJC} + 0.28 \sqrt{SJC} + 0.70 \ln ESR + 0.014 PtGA$, where TJC (number of painful joints), SJC (number of swollen joints) out of 28 evaluated joints: shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, knee; ESR - erythrocyte sedimentation rate according to the Westergren method; PtGA - the general assessment of patients' health status in millimeters on a 100-mm visual analogue scale (VAS) [5, 6]. Moreover, the definition of the DAS28ESR index is characterized by:

Obligatory assessment by the doctor of the patient's articular status (TJC and SJC) as a result of an individual examination.

- Obligatory individual assessment of patients with PtGA.
- Mandatory ESR assessment.
- Mandatory availability of computers.

Having spent the effort and time (5-8 minutes to assess the articular status), as well as the waiting time for ESR results within 1 hour, when determining the index, it is often possible to erroneously establish a higher degree of disease activity due to such a component as PtGA according to VAS, subjective an indicator that largely depends on concomitant pathology and to correct (in fact, unnecessary) drug treatment, which is not always indifferent to the patient, due to possible adverse reactions (ADR). In addition, doctors with different experience and qualifications work in routine practice, which will naturally affect the assessment of the inflammatory activity of RA. It should be noted that in 2007, at a meeting of the plenum of the board of the All-Russian public organization "Association

of Rheumatologists of Russia", a decision was made on the admissibility of using other methods for calculating RA activity, for which good comparability with DAS28 has been proven [5]. Further research is needed to confirm the potential usefulness of determining the NLR score as a diagnostic marker of systemic inflammation in RA.

Conclusions

The NLR index, calculated from the data of the general blood test, can be used in clinical practice as an objective and accessible marker of the inflammatory activity of RA.

Research transparency: The study was not sponsored. The authors are solely responsible for submitting the final version of the manuscript to print.

Declaration of financial and other relationships

All authors took part in the development of the concept of the article and in the writing of the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive royalties for the article.

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