Neutrophil/lymphocyte and platelet/lymphocyte ratios are associated with disease activity in rheumatoid arthritis

Nlr and Plr are reliable marker in rheumatoid arthritis

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Abstract

Aim: The aim of this study is to determine the relationship between Neutrophil to Lymphocyte (NLR) and Platelet to Lymphocyte (PLR) ratios in patients with Rheumatoid Arthritis (RA) and Disease Activity Score-28 (DAS28) and Rheumatoid Arthritis Quality of Life (RAQoL). Material and Method: One hundred twenty-five RA patients and 105 healthy controls were enrolled in the study. Patients were assessed and PLR, NLR, and DAS28, RAQoL values were calculated. Disease activity was calculated by DAS28 and quality of life was examined by RAQoL, HAQ (Health Assessment Questionnaire). Results: NLR (2,4 ± 1,9) and PLR (155,2 ± 82,3) value was significantly higher (p < 0.05) in RA. Positive correlation was observed between the two groups between DAS 28 with age, morning stiffness, VAS pain assessment, RF, ESR, CRP,NLR , PLR and swollen and tender joint number (p < 0.05) Significant negative correlation was observed between DAS 28 and hemoglobin, RBC, lymphocyte, monocyte % value (p < 0.05). There was no significant correlation between DAS28 and RAQoL, HAQ (p>0,05). Discussion: This study presents that NLR and PLR are associated with disease activity in patients with RA. NLR and PLR values can be assessed as an additional inflammatory marker in patients with RA.

Keywords

DAS-28; Neutrophil; Lymphocyte; Thrombocyte; Rheumatoid Arthritis, Hemogram

Introduction

Rheumatoid Arthritis (RA) is the most common inflammatory systemic disease all over the world. Its incidence is about 1%. Genetic and environmental factors play role in inanition and activation of RA. RA, not only affects joints but also extra-articular involvement is common [1-2]. This systemic disease can present major organ involvement. RA is one of the leading inflammatory diseases that reported mainly in females. In the nature of disease synovial inflammation leads to erosion and deformity in joints [2]. At baseline and during follow-up patients with RA is assessed by clinic examination including number of tender joint count (TJC), number of swollen and laboratory findings. And also visual analog scale (VAS), Disease activity score of 28 joints (DAS-28) is measured [3].

Hemogram, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most common laboratory tests in routine procedure. Chronic disease anemia is the most common laboratory finding. Anemia is associated with the disease activity in patients with RA. Hemogram also known as complete blood count is an available, cheap method that includes parameters of inflammatory, cardiovascular and oncologic diseases [4,5].

In the pathogenesis of RA, T and B lymphocytes, mast cells and neutrophils play an important role. Thus, it has been suggested that neutrophil/lymphocyte ratio (NLR) is a good indicator of systemic inflammation. And also the number of platelets in RA is high even in the early stages. Additionally, mean platelet volume (MPV) and platelet distribution width (PDW) are helpful markers [6-8].

Previous studies mentioned that NLR, PLR (platelet to lymphocyte), MPV and PDW are useful markers to measure systemic inflammation in RA [9-11]. But the data on these parameters is limited.

In this study, we aimed firstly, to assess NLR and PLR ratios and disease activity and quality of life in patients with RA. Secondly, the aim of this study is to describe hemogram parameters and its relation to RA.

Material and Methods

This study was performed between September 2017 and March 2018 and designed in Ahi Evran University Training and Research Hospital. The study design was performed retrospectively. One hundred twenty-five patients with RA, assessed by the diagnostic criteria of the American College of Rheumatology (ACR) 2010/ European League Against Rheumatism (EULAR) 2010 and a control group of 105 and gender-matched healthy subjects were enrolled in the study. Control group consists of healthy subjects from hospital staff. Demographic and clinical features were recorded. Routine tests including hemogram, ESR, CRP, Rheumatoid Factor (RF), Visual Analog Scale (VAS) (0-10), DAS28 and Larsen Score, swelling joint number, tender joint number, deformity, Rheumatoid Arthritis quality of life (RAQoL), Health Assessment Questionnaire (HAQ) were noted. Hemoglobin, Platelet, WBC (white blood cell), RBC (red blood cell), HCT (hemotcrite)

MCV (Mean corpuscular volume), MCH (Mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDW (red cell distribution), Neutrophil % (neutrophil percentage), lymphocyte % (lymphocyte percentage), Monocyte % (monocyte percentage), eosinophil % (eosinophil percentage), basophil % (basophil percentage), Neutrophil, lymphocyte, NLR, PLR, Eosinophil, Monocyte, Basophil, MPV (Mean platelet volume), PCT (plateletcrit), PDW values were recorded.

DAS28 were calculated by examination of 28 joints, ESR, patient VAS (0-10). Where O = best and 10 = worst, and both swollen and tender joint number. DAS28 scores is defined high (> 5,1), moderate (3,2<5,1), slightly active disease (≤ 3,2- > 2,6) and remission (≤ 2,6) respectively [12].

RAQoL is assessed in patients with RA to examine quality of life. It includes 30 questions with a yes/no (1/0) response [13]. HAQ is calculated for general health in RA [14].

Patients with uncontrolled hypertension and diabetes mellitus, hepatic, cardiac, renal insufficiency and decompensated obstructive pulmonary disease were excluded. Patients under corticosteroid treatment were also excluded. All measurements were taken by the same physician (SS). All patients received medical immunosuppressive treatment.

Written informed consent was obtained. The study was approved by the local ethics committee and in accordance with Helsinki Declaration. (Approval number: 2017-17/203).

Statistical analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data. Spearman correlation analysis was applied for correlation analysis using SPSS 22.0 program.

Results

The age and sex distribution of the patients in the case and control groups did not differ significantly (p > 0.05) (Table 1).

In the case group, hemoglobin value, RBC value, HCT value, lymphocyte% value, lymphocyte value, MPV value, PCT value were significantly lower than in the control group (p < 0.05). Such values as RBC value, MCV, MCH, RDW, NLR were significantly higher (p < 0.05) than PLR value in control group. In the case and control group, platelet value, WBC, MCHC, neutrophil, monocyte %, eosinophil % , basophil, neutrophil %, eosinophil, monocyte, basophil, PDW (p > 0.05) did not differ (Table 1). The clinical features of RA are given in Table 2.

Positive correlation was observed between the two groups between DAS 28 with age, morning stiffness, VAS pain assessment, RF, ESR, CRP, NLR and PLR and swollen and tender joint number (p < 0.05). Significant negative correlation was observed between DAS 28 and hemoglobin, RBC, lymphocyte, monocyte% value (p < 0.05). Significant correlation between DAS 28 and BMI, disease duration, platelet, WBC, HCT, MCV, MCH, MCHC, RDW, eosinophil%, basophil%, neutrophil, lymphocyte, eosinophil, monocyte, basophil, MPV, PCT, PDW were not observed (p > 0.05) (Table 3).

Table 1. Clinical and demographic features of Rheumatoid Arthritis and Healthy Control

		Patients (Rheumatoid Arthritis)			Controls			p	
Age		56,1	±	12,5	57,1	±	11,6	0,515	t
Sex	Women	95		76,6%	79		75,2%	0,808	X^2
	Men	29		23,4%	26		24,8%		
Hemoglobin (g/dL)		13,2	±	1,6	13,8	±	1,5	0,008	m
Platelet (10^3 u/L)		291,2	±	95,4	269,0	±	70,9	0,158	m
WBC (10^3 u/L)		7,4	±	2,4	7,7	±	1,6	0,050	m
RBC (10^6 u/L)		5,0	±	1,4	4,9	±	0,5	0,010	m
HCT (%)		39,7	±	5,3	41,9	±	4,2	0,001	m
MCV (fL)		87,0	±	8,2	86,0	±	4,9	0,028	m
MCH (g/dL)		28,7	±	3,3	28,3	±	2,2	0,036	m
MCHC (g/dL)		32,7	±	1,5	32,8	±	1,1	0,935	m
RDW (%)		14,9	±	2,3	13,6	±	1,3	0,000	m
Neutrophil %		59,6	±	10,2	57,2	±	9,9	0,076	m
Lymphocyte%		29,1	±	8,4	31,5	±	7,7	0,016	m
Monocyte %		7,6	±	2,7	7,4	±	1,9	0,970	m
Eosinophil %		2,4	±	1,5	2,1	±	1,5	0,089	m
Basophil %		0,8	±	0,5	0,7	±	0,3	0,221	m
Neutrophil (10^3 u/L)		5,1	±	6,2	4,5	±	1,3	0,563	m
Lymphocyte (10^3 u/L)		2,5	±	3,3	2,9	±	3,6	0,000	m
NLR		2,4	±	1,9	2,0	±	1,1	0,017	m
Eosinophil (10^3 u/L)		0,47	±	0,84	0,24	±	0,32	0,165	m
Monocyte (10^3 u/L)		0,83	±	1,66	0,57	±	0,17	0,078	m
Basophil (10^3 u/L)		0,1	±	0,2	0,1	±	0,1	0,313	m
MPV (f/L)		9,0	±	1,2	10,2	±	1,1	0,000	m
PCT (%)		0,25	±	0,08	0,27	±	0,07	0,006	m
PDW (fL)		12,1	±	2,4	12,5	±	2,3	0,415	m
PLR		155,2	±	82,3	117,7	±	48,1	0,000	m

t t-test / m Mann-Whitney u test / X^2 chi-square test

Table 2. Clinical features of Rheumatoid Arthritis

		N		%
Height		157,4	±	27,3
Weight		74,0	±	15,0
BMI (body mass index)		0,1	±	0,0
Disease duration		8,1	±	7,6
Morning Stiffness		24,6	±	23,9
VAS Pain		4,9	±	2,4
Onset joint involvement	Polyarticular	46		37,1%
	Oligoarticular	78		62,9%
DAS28		3,5	±	1,4
	Remission	32		25,8%
	Low	20		16,1%
	Moderate	58		46,8%
	High Activity	14		11,3%
Deformity				
None		85		68,5%
Swan Neck		16		12,78%
Thumb Z Deformity		2		0,12%
Ulnar Deviation		22		17,7%
Rheumatoid Nodule		9		7,3%

Discussion

This study suggests that hemoglobin, RBC, HCT, MCV, MCH, RDW, lymphocyte, NLR, MPV, PCT and PLR are significantly different in the RA group. While NLR and PLR are significantly higher, MPV is lower in patients with RA. Additionally, NLR, RAQoL, and PLR are associated with disease activity in patients with RA. But, we did not note any correlation between NLR and PLR with RAQoL. And also, neutrophil and platelet levels were not different from the control group.

Since past decades hemogram is assessed as a routine inflammatory test. Neutrophils are the leading elements in joint and synovial inflammation in patients with RA. And bone marrow is the main source of neutrophils [15].

It has been shown during systemic inflammation neutrophilia, leukocytosis, lymphopenia, thrombocytosis and elevated acute-phase reactants, TNF-α, IL-6, IL-8, procalcitonin are observed. ESR and CRP are simple and cheap biomarkers in systemic inflammation, but they are not specific. But also, measurements of proinflammatory cytokines are exhausting and precious (16). Serum of patients with RA is expected to have neutrophilia and lymphopenia. Although neutrophilia is explained by systemic inflammation, the cause of lymphopenia still cannot be understood [17]. In one article, lymphopenia has been reported to have a reduced number of T cells with 15% induration of RA but with a normal number of B-cells. The reduction in T-cell count in the study was reported to be caused by T- cells infiltrating the synovial membrane. The range of neutrophil and platelet levels was normal in RA because patients were receiving medical treatment [18].

The association between NLR and PLR in several diseases including cardiovascular, infectious and oncological disease has been shown [4,5]. It has been suggested that activated platelets lead to chronic inflammation which is related with atherogenesis [19].

In a study performed by Uslu et al, it was reported that NLR and PLR correlated with disease activity [20]. Furthermore, Kılıc et al. noticed that NLR and PLR levels are correlated with disease activity but not with RDW [21]. Tekeoglu et al. suggested that NLR is associated with disease activity. And also they noted that platelet count is associated with disease activity in RA, but they didn't measure PLR levels [22]. In this study, while NLR and PLR were associated with DAS28, but no correlation was observed between RDW and DAS28.

In RA patients, NLR has been reported to be a good indicator of response to tocilizumab treatment [23]. In a review of the treatment effect on laboratory parameters in Rigby et al. in RA patients, they concluded that all treatments, including biological agents, reduced serum neutrophil and platelet levels [24]. Koiwa et al. emphasized that NLR shows efficacy of biological treatments but is not a predictor of biological agent treatment [25]. The results of this study confirm the literature. But, none of the patients were receiving biological agent treatment. The association of MPV levels with platelets is well known. Proinflammatory cytokines suppress bone marrow, leading to a reduction in platelet volume. Kısacık et al. found low levels of MPV in the RA group [10]. In addition, Gasparyan et al. reported that the MPV levels were elevated during TNF-alpha blockade treatment [26]. Also, Yazıcı et al. reported that MPV levels are

Table 3. The relationship between DAS28 and clinical and laboratory parameters in patients with rheumatoid arthritis.

		Age	BMI	Disease Duration	Morning Stiffness	VAS Pain	RF	ESR
DAS28	r	0,204	-0,090	0,069	0,563	0,610	0,233	0,605
	p	0,023	0,351	0,443	0,000	0,000	0,009	0,000
		CRP	Larsen Score	Swollen Joint Number	Tender Joint Number	HAQ Score	RAQoL	Hemoglobin
DAS28	r	0,479	0,284	0,688	0,786	0,505	0,611	-0,258
	p	0,000	0,002	0,000	0,000	0,000	0,000	0,004
		Platelet	WBC	RBC	HCT	MCV	MCH	MCHC
DAS28	r	0,167	0,124	-0,249	-0,143	-0,016	-0,045	-0,144
	p	0,064	0,168	0,005	0,112	0,860	0,620	0,111
		RDW	Neutrophil %	Lymphocyte %	Monocyte%	Eosinophil%	Basophil %	Neutrophil
DAS28	r	0,026	0,223	-0,208	-0,193	0,046	-0,157	0,170
	p	0,771	0,013	0,020	0,032	0,613	0,081	0,059
		Lymphocyte	NLR	Eosinophil	Monocyte	Basophil	MPV	PCT
DAS28	r	-0,088	0,228	0,103	-0,061	-0,120	-0,133	0,103
	p	0,333	0,011	0,256	0,506	0,190	0,148	0,262
		PDW	PLR					
DAS28	r	0,042	0,205					
	p	0,820	0,022					

Spearman Correlation

correlated with disease activity in RA [9]. In this study, MPV levels were found to be low in the RA group but not in the relation to disease activity.

A report from Japan suggested that STEAP4 [Six-transmembrane epithelial antigen of prostate 4) expressed by neutrophils and monocytes regulates cell migration and depresses TNF-alpha. We found the percentage of monocytes associated with disease activity in our study. This may be due to the synthesis of STEAP4 from monocytes [27]. In recent studies, it has been reported that neutrophil extracellular traps increased in RA [28]. Additionally, an essential proinflammatory cytokine IL-17 is secreted by neutrophils [29].

There are some limitations in this study. Firstly, we did not note immune suppressive drugs and biologic agents. Secondly, we did not study STEAP4, neutrophil extracellular traps, and proinflammatory cytokines. Thirdly, the present study was performed as retrospective.

In conclusion, the major finding in this study NLR and PLR are associated with disease activity in RA. Similarly, NLR and PLR are good indicators to assess the disease activity in RA.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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