DOI: 10.24938/kutfd.1143318 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2023;25(1):56-63
Original Article *Özgün Araştırma*

A NEW INFLAMMATION MARKER IN RHEUMATOID ARTHRITIS: IMMATURE GRANULOCYTE

Romatoid Artritte Yeni Bir İnflamasyon Belirteci: İmmatür Granülosit

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ABSTRACT

Objective: This study aimed to reveal whether immature granulocyte levels can be used for determining the disease activity of rheumatoid arthritis.

Material and Methods: The study was conducted in the Kastamonu Rehabilitation Center. The data of 163 patients with rheumatoid arthritis were reviewed retrospectively. Laboratory data of 92 healthy individuals were used for the control group. Complete blood cell counts, measurement of erythrocyte sedimentation rate, and C-reactive protein level were used for the laboratory assessments. The individuals with active infection and any hematological, cardiovascular, metabolic disorder, malignancy, history of trauma, surgery, and hospitalization within the last 15 days were excluded from the study.

Results: We found that the number and percentage of immature granulocyte were significantly higher in the patient group ($p<0.05$). A positive correlation was found between immature granulocyte and erythrocyte sedimentation rate ($r=0.171$ $p=0.03$), immature granulocyte and C-reactive protein ($r=0.321$ $p<0.001$) in the patient group. In the rheumatoid arthritis group, the number and percentage of immature granulocytes were statistically significantly higher in patients with C-reactive protein >5 than those with C-reactive protein ≤ 5 ($p<0.05$).

Conclusion: The immature granulocytes can be a rapid, easily accessible and cost-effective parameter that indicates inflammation in rheumatoid arthritis. It may be useful to use this parameter in the evaluation of disease activity.

Keywords: *Rheumatoid arthritis, immature granulocyte, disease activity.*

ÖZ

Amaç: Bu çalışmanın amacı immatür granülosit sayısının, romatoid artritte hastalık ativitesini gösteren bir belirteç olup olmadığını ortaya koymaktır.

Gereç ve Yöntemler: Çalışmaya, Kastamonu Rehabilitasyon Merkezi'nde romatoid artrit tanısı ile takipli 163 hasta alındı. Hastaların verileri, laboratuar bilgi sisteminden bulundu. Kontrol grubu için 92 sağlıklı bireyin laboratuvar verileri kullanıldı. Aktif enfeksiyonu, hematolojik, kardiyovasküler, metabolik ve malign hastalığı olan hastalar ile son 15 gün içinde travma, cerrahi girşim ve hastaneye yatış öyküsü olanlar çalışma dışı bırakıldı.

Bulgular: Hasta grubunda immatür granülosit sayısı ve yüzdesinin anlamlı olarak daha yüksek olduğunu bulundu ($p<0.05$). Hasta grubunda immatür granülosit ile eritrosit sedimentasyon hızı ($r=0.171$ $p=0.03$), ve C-reaktif protein ($r=0.321$ $p<0.001$) arasında pozitif ilişki saptandı. Yine hasta grubunda grubunda, immatür granülosit sayısı ve yüzdesi, C-reaktif protein düzeyi >5 olan hastalarda, C-reaktif protein düzeyi <5 olanlara göre istatistiksel olarak anlamlı derecede yüksekti ($p<0.05$).

Sonuç: İmmatür granülosit seviyesi, romatoid artritte inflamasyonu gösteren hızlı, kolay erişilebilir ve uygun maliyetli bir belirteç olabilir.

Anahtar Kelimeler: *Romatoid artrit, immatür granülosit, hastalık aktivitesi.*

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Received / Geliş Tarihi: 12.07.2022 **Accepted** / Kabul Tarihi: 16.01.2023

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Doi: 10.24938/kutfd.1143318

INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis, affecting ~1% of the general population worldwide (1). In addition to being a chronic, autoimmune and systemic disease qualified by synovial inflammation, it can cause damage to the joints, particularly in cases where inflammation is permanent. Although there is no definite information about the pathological processes that cause the emergence of RA, it contains a balance between genetic risks and environmental factors. If the inflammatory process that leads to the formation of RA is left uncontrolled, it will injure the joints and cause disability (2). RA disease can cause consequences such as disability, bone erosion, cartilage damage, morbidity, and mortality. Early detection and treatment of the disease are important to prevent functional impairment from reaching advanced stages (3). The management of the disease is carried out by meticulous and ceaseless follow-up of the markers and laboratory data, except for clinical symptoms (4). The acute phase reactions, ache, tender-swollen joints, and global Visual Analog Scale (VAS) evaluations made by patients and physicians are used for the RA disease activity measurement (5). For this purpose, the 2 most commonly used tests are the erythrocyte sedimentation rate (ESR) and the serum C reactive protein (CRP) concentration, both of which increase inflammation.

Neutrophils, mast cells, and B and T lymphocytes all have specific roles in the pathogenesis of RA, and they differ according to inflammation in RA (6). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are among the indicators handled in the measurement of disease activity in RA (7, 8). With the development of new hematology analyzers, early detection of inflammation has become possible (9). The immature granulocyte percentage (IG%), a new inflammatory marker, is not yet known enough (10). Recent studies have proven that the IG% increases earlier than the traditional parameters like CRP and leukocyte count in inflammatory states such as infection and sepsis (11). Immature granulocyte (IG) cells do not exist in peripheral blood under physiological circumstances. The detection of IG in peripheral blood that does not expect to be seen in healthy people is a sign of bone marrow activation (12). The IG% and the immature granulocyte count (IGC) are novel inflammatory markers easily obtained with automated hematology analyzers at complete blood count (11). Inflammatory processes have a pivotal function in RA pathogenesis (13). Therefore, immature granulocyte count, which is an inflammation marker, can be used for identifying RA disease activity. It may be advantageous to obtain objective data that correlates with the disease activity of RA from whole blood cell analysis. It may be functional to access concrete data on the disease activity of RA through complete blood cell analysis. The study will be the first to assess IG in patients with RA. It is aimed to reveal whether IGC can be used as a sign in the determination of disease activity in RA.

MATERIALS AND METHODS

This study, which was designed retrospectively, was approved by Kastamonu University Clinical Research Ethics Committee with the decision of 2020-KAEK-143-108. Patients who presented to the Kastamonu Rehabilitation Center Physical Medicine and Rehabilitation outpatient clinic between January 2020 and December 2020 and were diagnosed with RA in accordance with the American College of Rheumatology (ACR) 2010 criteria were included in the patient group (14). Patients who had no inflammatory joint disease and had normal ESR and CRP values during the study period were included as the control group. In both groups; patients with a history of infection, malignancy, trauma, surgery, hospitalization within the last 15 days and those with a metabolic hematological disease, and pregnant and breastfeeding women were excluded from the study. Demographic information and laboratory data of the patients were obtained from the hospital Laboratory Information System (LIS). Complete blood count (CBC) parameters were calculated with an automated hematological analyzer (XN–1000–Hematology–Analyzer–Sysmex

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Corporation, Japan). White blood cell (WBC), platelet distribution width (PDW), mean platelet volume (MPV), neutrophil count (NEUTC), eosinophil count (EOC), basophil count (BASOC), neutrophil percentage (NEUT%), lymphocyte percentage (LYMPH%), monocyte percentage (MONO%), IG count (IGC) and IG percentage (IG%) values were calculated from CBC data. The auto-analyzer enables to detection of IG% and IGC using flow cytometry in the DIFF channel. Forward-scattered light, lateral-scattered light, and lateral fluorescent light are used to detect volume, complexity, and DNA/RNA content. The NLR, PLR, and systemic inflammatory index (SII) values were calculated using the relevant formulas. The patient group was divided into two subgroups, the patients with CRP≤ 5 and those with CRP>5. The data obtained were then compared between the two groups. The IG numbers and percentages were compared between the two groups. CRP was analyzed with COBAS e411 (Roche Diagnostics, Mannheim, Germany). ESR was analyzed with ASL-100 (ALARIS Medikal, Turkey).

Statistical analysis of the data was made using the "Statistical Package for Social Sciences version 18.0 for Windows" (SPSS Inc., Chicago, USA) program. Descriptive statistics of were given as number and percentage (%) for categorical variables and median (25^{th} Percentiles, 75^{th} Percentiles) for numerical variables. The Mann-Whitney U test was used to compare the data between the control group and the RA groups, as the results did not fit the normal distribution. A Chi-square test was performed to compare the groups according to age and gender. Receiver Operating Characteristic (ROC) analysis and Youden's index were made for determining Area Under Curve (AUC), cut-off, sensitivity, and specificity values. Spearmen's Correlation Test was used to analyze the relationship between the hematological and biochemical parameters of RA patients and IG. P <0.05 was interpreted for deciding if the results were statistically significant.

RESULTS

Since our study was retrospective, the data of the patients who applied to our hospital during the active periods of the disease were obtained from the laboratory information system. The study was conducted with a total of 163 people for the patient group and 92 people for the control group. No significant difference was identified between the groups according to age. The gender distribution and average age of our patients are shown in Table 1.

Table 1: Some Laboratory and Demographic Data in RA Patients (n=163)

Age (median±ss)	57.17 ± 12.11
Sex (Female, %)	138/163=85%

RA: Rheumatoid arthritis

It was concluded that the number and percentage of IG, ESR, and CRP levels, NLR and PLR ratios, and SII values were significantly higher in the patient group (p <0.05) (Table 2).

In addition, the hemoglobin level was significantly lower, while the neutrophil count and the platelet count were significantly higher in the patient group (Table 2) As the patient group was divided into two groups: CRP ≤ 5 and CRP >5. In the CRP >5 groups, the number and percentage of IG were higher at a significant degree (p<0.05) (Table 3).

A positive correlation was found between IG and ESR (r=0,171 p=0.03), IG and CRP (r=0,321 p<0.001), IG and WBC (r=0,629 p<0.001), IG and PLT (r=0,219 P=0.005) and IG and NEUTC (r=0,641 P<0,001) in the patient group. A negative correlation (r=-0.441 p<0.001) was found between IG and LYMPH. ROC curves were used to determine the effectiveness of laboratory variables used in the diagnosis of RA (Figure 1). The prediction ability of ESR and CRP to diagnose RA was significant (p<0.001)(Table 4). No significant area under curve (AUC) value was found for the IG level in the ROC analysis.

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Table 2: Comparison of tests of RA patients and control group with Mann Whitney U test

	Control (92)	Patient (163)	p
	Median (IQR)		
WBC	6.33 (5.4-7.6)	6.97 (5.87-9.11)	0.001
RBC	4.82 (4.56-5.10)	4,67 (4.35-5.02)	0.010
HGB	13.5 (12.6-14.3)	12.8 (12.0-13.6)	<0.001
HCT	40.2 (38.0-42.1)	39.0 (36.5-41.2)	0.002
PLT	261.5 (216-295)	281 (235-333)	0.015
RDW_SD	40.3 (38.7-42.2)	42.6(40.1-45.2)	<0.001
NRBC#	0.01(0.01-0.01)	0.01 (0.01-0.02)	0.009
NEUT#	3.5 (3.0-4.6)	4.2 (3.2-5.9)	<0.001
MONO#	0.45 (0.41- 0.55)	0.57 (0.44-0.70)	<0.001
LYMPH%	33.1 (28.1-38.5)	28.7 (21.5-36.4)	<0.001
IG#	0.01(0.01;0.02)	0.01(0.01;0.03)	0.004
IG%	0.2 (0.1-0.2)	0.2 (0.1-0.3)	0.022
MicroR	2.4 (1.5-4.4)	3.6 (2.2-6.7)	0.001
NLR	1.7 (1.35-2.21)	2.08 (1.46-3.07)	<0.001
PLR	124 (99-150)	134 (106-175)	0.013
SII	439 (320-610)	551 (355-961)	<0.001
ESR mm/h	14 (12-18,75)	21.5 (13-36)	<0.001
CRP mg/L	3.15 (1.9-5.0)	6.52 (2.9-17.2)	<0.001

WBC: White Blood Cell, RBC: Red Blood Cell, HGB: Hemoglobin, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, PLT: Platelets, RDW: *Red Cell Distribution Width* SD: Standard Deviation, NRBC: Nucleated Red Blood Cell, NEU: Neutrophil, LYMPH: Lymphocyte, IG: İmmature Granulocyte, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, SII: Systemic Inflammatory Index, ESR: Erythrosir Sedimentation Rate, CRP: C- Reactive Protein) (Normal value is CRP (0-5) mg/L, ESR (0-20) mm/saat

Table 3: Comparison of RA patients with CRP values below 5 and above 5 with Mann Whitney U test

	CRP 0-5 (68)	CRP >5 (95)	p
	Median (IQR)		
WBC	6.39 (5.56;7.96)	7.82 (6.20;9.94)	<0.001
MCH	28.85 (26.8;29.0)	27.3 (25.5;28.7)	0.05
MCHC	33.2 (32.5;34.0)	32.7 (32.1;33.5)	0.008
PLT	269 (223;307)	291 (241;357)	0.025
NEUT#	3.5 (2.95;4.77)	4.2 (3.55;6.78)	<0.001
MONO#	0.50 (0.41;0.65)	0.61 (0.48;0.76)	0.004
NEUT%	55.2 (50.6;62.3)	63.1 (56.1;71.2)	<0.001
LYMPH%	33.7 (26.8;37.9)	25.7 (19.6;32.4)	<0.001
IG#	0.01 (0.01;0.02)	0.02 (0.01;0.03)	0.001
IG%	0.2 (0.1;0.27)	0.2 (0.1;0.4)	0.016
MicroR	3.0 (2.0;5.4)	4.1 (2.3;7.7)	0.046
NLR	1.65 (1.31;2.29)	2.45 (1.73;3.60)	<0.001
PLR	127 (98;158)	139 (110;185)	0.019
SII	411 (308;632)	724 (423;1143)	<0.001
ESR	16 (10;23)	29 (18;45)	<0.001
CRP	2.64 (1.24;3,73)	14 (7,6;23,4)	<0.001

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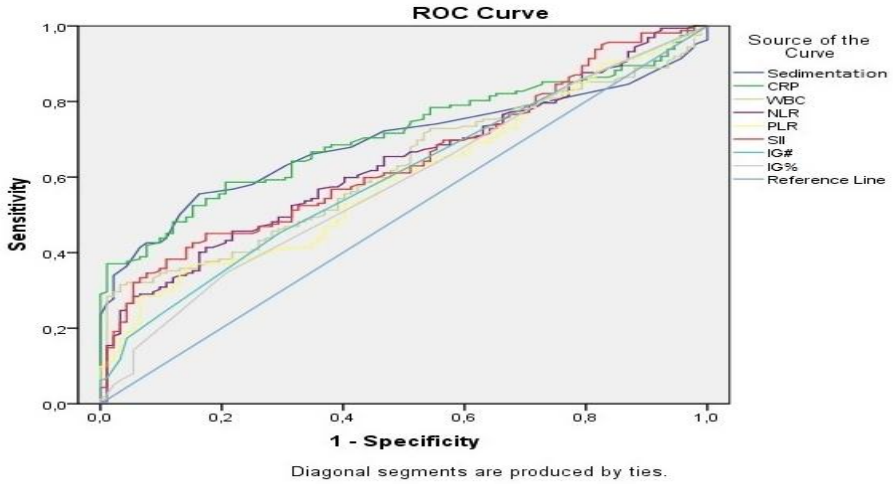

Figure 1. ROC curve analysis of some hematological data in RA patients

Table 4 : Roc analysis values of sedimentation and CRP tests in RA patients

	Cut-off	AUC	95%CI	p	Sensivite%
ESR(mm/h)	20.5	0.691	0.62-0.75	<0.001	55
CRP	1.9	0.709	0.64-0.77	<0.001	85

(ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein)

DISCUSSION

In this study, the relationship between disease activity and IG values in RA patients was examined. The findings obtained in the study proved that IG levels were higher in patients diagnosed with RA. The function of hematological markers in the assessment of inflammatory joint diseases is still under investigation. This study is the first to evaluate the levels of IG in RA. IGC refers to the sum of promyelocyte, myelocyte, and metamyelocyte cells that mature along with the myeloid series from the multipotent stem cells located in the bone marrow. The bone marrow regulates the production of immature granulocytes in response to inflammatory signals. Although the mechanisms of this regulation are obscure, IG% has been considered as a new CBC parameter to predict inflammation (9). In their study, Ansari et al. concluded that all immature granulocytes may increase in inflammatory disease and this may be more pronounced in the peripheral enthesitis of the inflammatory lower extremities, rather than of a mechanical nature (15). Similarly, IG level was concluded higher in the RA patient group.

Hemogram variables, particularly the ones that include immune system components, have a critical function in the evaluation of different illnesses such as RA (16). It has been mentioned in many studies that neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are parameters showing disease activity (7,8,13). We also reached to the result that NLR and PLR were significantly higher in the patient group. However, IG level is a simpler and easier to obtain parameter than NLR and PLR. Different hemogram variables used in RA are platelet and lymphocyte counts. The relationship between increased thrombocytosis and disease activity in RA has been known for many years (17). It is thought that lymphocytes undergo apoptosis in RA. Both thrombocytosis and lymphopenia are associated with inflammatory cytokines (16). In our study, there was a positive correlation between IG level and platelet count while there was a negative correlation with lymphocyte count. This result supports the hypothesis that IG level indicates inflammation and disease activity in RA.

Although ESR and CRP are not specific to the disease, their high levels suggest active disease (18, 19). In our study, IG level was correlated with ESR and CRP levels

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that are the most commonly used inflammatory markers to evaluate disease activity. Also, Ansari et al showed that CRP and IG levels were correlated in patients with peripheral enthesitis (15). It is not possible to measure the disease activity by using a sole parameter for all of the patients with rheumatoid arthritis (RA). Disease Activity Score-28 (DAS28) was formed for measuring disease activity in RA (20). Prospective studies are needed to compare IG level and DAS 28 scores.

IGC ve IG% has been used as an inflammation marker in many diseases. According to Nierhaus et al., the total number of IG in peripheral blood from intensive care can be effectively used for deciding the infected and non-infected patients with systemic inflammatory response syndrome quite early (24). Our study showed that IG level was an indicator of inflammation in RA. However, with this retrospectively designed study, we can not argue that the IG level is an early inflammatory marker in RA. Nevertheless, the lack of a strong correlation between IG and CRP may be related to the fact that IG is an earlier inflammatory marker. Further prospective studies are needed on this subject.

Ünal Y. has emphasized that IG value is a reliable parameter both in recognition of acute appendicitis and deciding simple or complicated appendicitis (12). In another study, Ünal et al demonstrated that an increased IG% is an easy, rapid, and useful indicator for diagnosing acute necrotizing pancreatitis early (22). The mechanism by which IG, an inflammation marker, is so sensitive and specific for acute abdominal pathologies is still unclear. We could not obtain such a striking result for RA in our study. According to the ROC analysis, the IG level was not specific and sensitive for RA. However, any gold standard is not still accepted as an inflammatory marker for RA (23, 24). We believe that the IG level for RA can be used in the follow-up of disease severity rather than being sensitive and specific for the disease.

The cost of follow-up and treatment of RA patients is high (25). Therefore, it may be very wise to evaluate disease activity with a single hemogram tube. In addition, in units where laboratory services are not sufficient, it may be considered to use the IG level to evaluate for disease activity in RA.

It is known that granulocytes have an important function in the pathophysiology of autoimmune diseases such as RA. The main role of granulocytes in pathophysiology is to secrete inflammatory cytokines and immunomodulatory molecules. Especially low-density granulocytes (LDG) secrete more cytokines than high density (HDG) ones (26). According to Wright et al., RA LDGs differ from RA neutrophils in function (26). They stated that the release degree of receptors for cytokines, especially tumor necrosis factor receptors (TNFRs), was lower in RA LDGs compared with RA neutrophils, and this caused a decrease in the response to tumor necrosis factor alfa (TNF-α) in culture. Determining the level of LDG requires a series of laborious and expensive molecular steps (26,27). However, Wright et al. emphasized that RA LDGs were representative of an immature population of neutrophils in the peripheral context. Therefore, IG levels in peripheral blood may be more important than we think for the disease characterized by increased TNF-a signaling and it may contribute to the explanation of the causes of the lack of response observed in anti-TNF therapy in some patients with RA. In addition, it may also be an indicative marker that will be used in cases where there is no response to anti-TNF therapy. We believe that our study, which is the first about IG levels in RA, will inspire future studies on this subject.

This study has several limitations. First, it was a retrospective, single-center study. More importantly, the DAS28 score could not be used. Since our study was designed retrospectively, sufficient data could not be obtained to calculate the DAS 28 score in the patient files. Despite this deficiency, we think the study will increase interest in studies on the use of IG levels in rheumatological diseases.

In conclusion,immature granulocyte level can be used as a laboratory parameter indicating disease activity in RA. Its most important advantages are being fast, easily available, and cost-effective. It can be considered to be used to evaluate disease activity in cases where other

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laboratory parameters cannot be measured. The IG levels in peripheral blood indicating LDG level may be important in terms of prognosis and response to anti-TNF therapy. However, prospective controlled studies in patients with RA are needed. Despite its limitations, we believe that the study will draw attention to the level of IG in inflammatory joint diseases and will be a guiding pioneer for further studies.

Conflict of Interest: The author has no conflict of interest to declare.

Support and Acknowledgment: There is no funding source.

Researchers' Contribution Rate Statement:
Concept/Design: EÖ,SG; Analysis/Interpretation: EÖ,SG; Data Collection: EÖ,SG; Writer: EÖ,SG; Critical Review: EÖ,SG; Approver : EÖ,SG

Ethics Committee Approval: The ethics committee approval of the study was obtained from the Kastamonu University Clinical Research Ethics Committee (Date:08.09.2021 / Decision no: 2020-KAEK-143-108)

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