Evaluation of Neutrophil to Lymphocyte Ratio and Monocyte to Lymphocyte Ratio in Gouty Arthritis Attacks

A Şahin[1], AU Uslu[2], D Seven[3], A Camcı[1], Ö Demirpençe[4], M Şahin[4], T Uncu[3], B Aydın[5]

ABSTRACT

Objective: To evaluate neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio (MLR) in patients with gouty arthritis.

Methods: Forty-five patients with gout and 45 healthy age and gender matched individuals, were included in this study. Clinical and laboratory data of patients during acute gouty arthritis (AGA) attack period, as well as in remission and control group data were reviewed and recorded from medical files. Patients were divided into two groups as having the arthritis attack and in remission.

Results: NLR values were 4.19±3.37 in AGA patients, 2.64±1.74 in patients in remission, and 2.07±1.01 in controls. NLR values in AGA were higher than patients in remission and controls, whereas there was no difference between patients in remission, and controls ($p<0.0001$, $p<0.0001$, $p=0.453$; respectively). MLR values were 0.36±0.21 in AGA patients, 0.25±0.15 in patients in remission, and 0.22±0.06 in controls.MLR was higher in AGA patients than patients in remission, and controls, but there was no difference between patients in remission and healthy individuals ($p<0.0001$, $p<0.0001$, $p=0.604$; respectively). NLR and MLR values in AGA patients had positive correlations with CRP, ESR and leukocyte count. Thecut-off value of NLR was2.18 in ROC analysis (73% sensitivity, 63% specificity, AUC 0.676; $p=0.004$). The cut-off value of MLR was 0.22 in ROC analysis (62% sensitivity, 54% specificity, AUC 0.655; $p=0.011$).

Conclusions: We concluded that MLR and NLR could be used as a cheap and useful inflammatory marker predicting arthritis attacks in patients with gout.

Keywords: Arthritis attack, gout, inflammation, monocytes-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio

---

From: [1]Department of Internal Medicine - Rheumatology, Medical School, Cumhuriyet University, Sivas, Turkey. [2]Internal Medicine Clinic, Eskisehir Military Hospital, Eskisehir, Turkey. [3]Department of Internal Medicine, Medical School, Cumhuriyet University, Sivas, Turkey. [4]Department of Biochemistry, Medical School, Cumhuriyet University, Sivas, Turkey. [5]Internal Medicine Clinic, Etimesgut Military Hospital, Ankara, Turkey.

Correspondence: Dr A Sahin, Department of Rheumatology, Cumhuriyet University School of Medicine, 58140, Sivas/ Turkey. E-mail: dralsahin@hotmail.com

INTRODUCTION

Gout disease is an auto-inflammatory disease caused by accumulation of monosodium urate crystals (MSU) in tissues and organs due to hyperuricemia. Although it is encountered in male patients with advanced age, it affects more than 1/100 of general population in the world (1, 2). The disease has four stages such as asymptomatic hyperuricemia, detection of MSU without any signs or symptoms, acute gouty arthritis, and advanced stage gout-chronic tophaceous. Acute gouty arthritis (AGA) may develop without any organ damage sign after nearly 15-20 years' of asymptomatic hyperuricemia (3-5). AGA develops due to accumulation of MSU within joints and in adjacent tissues, and it has generally a monoarticular presentation. It commonly involves the big toe, and ankle, knee in decreasing order, whereas it involves fingers and elbows in advanced stages. Severe pain, swelling, increased heat, and erythema may be observed in involved joints (4, 5). Due to effects of MSU crystals, sequential activation of immune system and mechanisms are observed (6).

Whole blood count is a commonly ordered test evaluating immune system elements in daily clinical practice. Neutrophils, lymphocytes, and monocytes play a role in AGA pathogenesis directly or indirectly and/or via complex interaction between them (6-8). Ratios between these immune system elements (neutrophil to lymphocyte ratio and monocyte to lymphocyte ratio) have been listed in inflammatory markers which have been used more frequently recently. There are many studies performed in neutrophil to lymphocyte ratio (NLR) in many diseases such as ankylosing spondylitis (AS) (9), primary Sjögren's syndrome (pSS) (10), rheumatoid arthritis (RA) (11), and familial Mediterranean fever (FMF) (12). Studies performed in monocyte to lymphocyte ratio (MLR) are quite limited in number, and they have been performed mainly in infectious diseases such as tuberculosis (13, 14).

The present study is the first one performed to evaluate the predictive value of NLR and MLR in gouty arthritis attacks. The aim of the study was to measure NLR and MLR values in

gout patients at AGA and in remission and to determine availability of these markers in clinical practice and as laboratory tests.

MATERIALS AND METHODS

The present study was performed between May 2014 and February 2015. 45 patients diagnosed with gout disease, and 45 age and gender matched healthy individuals were enrolled in the study. Clinical and laboratory data of patients during AGA attack period, as well as in remission and control group data were reviewed and recorded from medical files. Patients were divided into two groups as having the arthritis attack and in remission. The Local Ethics Committee for Clinical Research approved the study. In addition, the study was carried out in accordance with the principles of the Declaration of Helsinki.

Patients who were diagnosed with diabetes mellitus, hypertension, acute and/or chronic infection, malignancy, and received corticosteroid treatment in the last 3 months, were excluded from the study. All blood samples were studied within less than one hour after the sampling. The complete blood counts have been performed in the same analyzer, Mindray BC-6800, which is routinely checked every month in the central laboratory of our institution.

Statistical analysis

The Statistical Package for Social Sciences for Windows 14.0 (SPSS, Inc, Chicago, USA) was used for statistical analyses. Continuous variables were presented as mean ± standard deviation, mean; while categorical variables were indicated as number (n) and percent (%). Variables meeting the parametric assumptions were assessed using *t*-test and one-sided ANOVA test in independent groups, Tukey HSD test in the inter-group post-hoc evaluation, while categorical variables were reviewed by *chi-square* test. Pearson correlation analysis

was used to test the correlation of the data. ROC curve graphics were carried out in the computation of sensitivity and specificity. *P* values of under 0.05 were accepted as significant.

RESULTS

Of gout patients, 30 (66.7%) were males, and 15 (33.3%) were females with the mean age of 60.8±12.0 years. Of the control group, 26 (57.8%) were males, and 19 (42.2%) were females with the mean age of 56.2±10.3 years. There was no significant difference in gender and age between two groups (p=0.387 and p=0.052, respectively).

NLR values were 4.19±3.37 in patients with AGA, 2.64±1.74 in gout patients in remission, and 2.07±1.01 in the control group. NLR value in AGA patients was higher than the patients in remission and in the control group (p<0.0001 and p<0.0001, respectively), whereas there was no difference in NLR value between patients in remission and the control group, (p=0.453) (Table 1) (Figure 1). MLR values were 0.36±0.21 in AGA patients, 0.25±0.15 in patients in remission and 0.22±0.06 in controls. MLR value in AGA patients was higher than the patients in remission and in the control group (p<0.0001 and p<0.0001, respectively), whereas there was no difference in MLR value between patients in remission and the control group (p=0.604)(Table 1)(Figure 2). Other laboratory results of AGA patients, patients in remission and control group are summarized in Table 1 and 2.

Positive correlations were determined between NLR, MLR values and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leukocyte in patients with AGA (Table 3 and 4). The cut-off value of NLR was2.18in the ROC analysis with sensitivity of 73%, specificity of 63%, and AUC of 0.676 (95% Cl 0.542-0.769, p=0.004)(Figure 3). The cut-off

value of MLR was 0.22 in the ROC analysis with sensitivity of 62%, specificity of 54%, and AUC value of 0.655 (95% Cl 0.563-0.789, p=0.011) [Figure 3].

DISCUSSION

In the present study, relationship between arthritis attack and NLR, MLR values in gout patients was evaluated. Our findings indicated that NLR and MLR values were higher in gout patients with arthritis attack than patients in remission and in the control group. There was no difference in values between in remission period and control group. It was observed that NLR and MLR values were correlated with CRP, ESR, and leukocyte during arthritis attack.

Neutrophil, lymphocyte, and monocytes which are immune system elements, have active roles in inflammatory process, and they have some changes during this process. In tissue damage, neutrophils and monocytes act in functions such as antigen presentation and processing, phagocytosis, as well as providing contributions in immune system activation by releasing inflammatory cytokines and free oxygen radicals (15, 16). Lymphopenia may be caused by increased stressor hormones during inflammatory process, and increased apoptosis (17). In recent years, ratios between these immune system elements have been frequently used as cheap, practical, and helpful inflammatory markers.

There are studies performed about NLR in patients with AS, pSS and FMF. Those studies were concentrated mainly in active disease period, disease activity, or the relationship with other inflammatory markers. Gokmen at al. (9) showed that NLR values were higher in AS patients than the control group, and there was a correlation between NLR and CRP levels. Hu et al. (10) reported that NLR values in pSS patients were higher than the control group, and they had positive correlation with Sjögren's syndrome disease activity index. Celikbilek

et al. (12) showed that NLR values were higher in FMF patients having an attack than FMF patients without the attack and the control group.

Studies performed about MLR values are limited to infectious diseases. When immune reactions in infectious diseases are considered, roles of monocyte and lymphocytes and their reflections in peripheral blood are important. Wang et al. (13) indicated that MLR values were higher in patients with active tuberculosis than healthy individuals. Naranbhai et al. (14) reported in their study that elevated MLR values were correlated with tuberculosis and mortality.

It is believed that synovial infiltration of neutrophils and monocytes is important in disease pathogenesis and progression in RA patient. Increased lymphocyte apoptosis may cause lymphopenia in RA patients (11, 18). Uslu et al. (11) reported that NLR values in RA patients were higher than the control group, and were correlated with disease activity score-28. Kawanaka et al. (18) showed in their study that monocyte subgroups ($CD14^+$, $CD16^+$) were higher in RA patients than the control group.

In gout patients, MSU crystals cause inflammation in joints and activation of immune system elements (neutrophils and monocytes), which provide release and control of proinflammatory cytokines. These cytokines contribute into activation of neutrophils and monocytes (19-21). Meanwhile when MSU effects and presence of systemic inflammation are evaluated together with effects of stressor hormones such as cortisol on the immune system, and their reflection in peripheral blood, the end result may be lymphocyte apoptosis and lymphopenia. In AGA patients, effects of cortisol and on the immune system may end up with neutrophilia and lymphopenia (15, 20). Urano et al. (22) showed that cortisol levels of AGA patients were correlated with interleukin-6 and CRP values.

The present study is the first one evaluating NLR and MLR values in gout patients, and investigating the correlation between those values and AGA. MSU effects imply that

inflammatory markers made up of these components, such as NLR and MLR, may cause some changes in AGA. As NLR and MLR values were higher in AGA patients when compared with patients in remission and controls, and they had correlations with other inflammatory markers, then this suggested a possible correlation with AGA.

The present study has also some limitations, which are retrospective study design, and low number of enrolled patients. As we know, uric acid levels can be normal in gouty arthritis attacks. For this reason, we did not compare the levels of uric acid of the subjects.

In conclusion, the present study indicated that NLR and MLR values might be two new inflammatory markers which might be used in AGA evaluation in gouty patients with arthritis attacks.

ACKNOWLEDGEMENTS

We would like to thank to Roche-Turkey for helping us in editing of this manuscript.

Conflict of interest: There is no conflict of interest in the present study.

REFERENCES

1. Ar'ev AL, Kunitskaia NA KL. Gout and hyperuricemia today: prevalence, risk factors, features in the elderly. Adv Gerontol. 2012;25:540–544.
2. Pétrilli V, Martinon F. The inflammasome, autoinflammatory diseases, and gout. Jt Bone Spine. 2007;74:571–576.
3. Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis. 2014;13:1598–1600.
4. Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. Postgr Med. 2012;124:98–109.
5. Perez-Ruiz F, Castillo E, Chinchilla SP, Herrero-Beites AM. Clinical manifestations and diagnosis of gout. Rheum Dis Clin North Am. 2014;40:193–206.
6. Dalbeth N, Haskard DO. Mechanisms of inflammation in gout. Rheumatology (Oxford). 2005;44:1090–1096.
7. Steiger S, Harper JL. Mechanisms of spontaneous resolution of acute gouty inflammation. Curr Rheumatol Rep. 2014;16:392.
8. Busso N, So A. Mechanisms of inflammation in gout. Arthritis Res Ther. 2010;12:206.
9. Gökmen F, Akbal A, Reşorlu H, Gökmen E, Güven M, Aras AB, Erbağ G, Kömürcü E, Akbal E, Coşar M. Neutrophil-Lymphocyte Ratio Connected to Treatment Options and Inflammation Markers of Ankylosing Spondylitis. J Clin Lab Anal. 2014 May 21. doi: 10.1002/jcla.21768.
10. Hu ZD, Sun Y, Guo J, Huang YL, Qin BD, Gao Q, Qin Q, Deng AM, Zhong RQ. Red blood cell distribution width and neutrophil/lymphocyte ratio are positively correlated with disease activity in primary Sjögren's syndrome. Clin Biochem. 2014;47:287–290.
11. Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, Bağcacı S, Küçükşen S. Two New Inflammatory Markers Associated with Disease Activity Score-28 in

Patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheum Dis. 2015 Apr 21.doi: 10.1111/1756-185X.12582. [Epub ahead of print].

12. Celikbilek M, Dogan S, Akyol L, Borekci E, Zararsiz G, Kozan M, Gunaydın I. Neutrophil-Lymphocyte Ratio in Patients With Familial Mediterranean Fever. J Clin Lab Anal. 2015;29:80–83.
13. Wang J, Yin Y, Wang X, Pei H, Kuai S, Gu L, Xing H, Zhang H, Huang Q, Guan B. Ratio of monocytes to lymphocytes in peripheral blood in patients diagnosed with active tuberculosis. Braz J Infect Dis 2014Dec 18. pii: S1413-8670(14)00214-1. doi: 10.1016/j.bjid.2014.10.008
14. Naranbhai V, Kim S, Fletcher H, Cotton MF, Violari A, Mitchell C,Nachman S, McSherry G, McShane H, Hill AV, Madhi SA. The association between the ratio of monocytes:lymphocytes at age 3 months and risk of tuberculosis (TB) in the first two years of life. BMC Med. 2014;12:120.
15. Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. Int Immunopharmacol 2010;10:1325–1334.
16. Parihar A, Eubank TD, Doseff AI. Monocytes and macrophages regulate immunity through dynamic networks of survival and cell death. J Innate Immun. 2010;2:204–15.
17. Uslu AU, Deveci K, Korkmaz S, Aydin B, Senel S, Sancakdar E, Sencan M. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial mediterranean fever? Biomed Res Int. 2013;2013:185317.
18. Kawanaka N, Yamamura M, Aita T, Morita Y, Okamoto A, Kawashima M,Iwahashi M, Ueno A, Ohmoto Y, Makino H. CD14+,CD16+ blood monocytes and joint inflammation in rheumatoid arthritis. Arthritis Rheum. 2002;46:2578–2586.

19. Martin WJ, Harper JL. Innate inflammation and resolution in acute gout. Immunol Cell Biol.2010;88:15–19.

20. Pouliot M, James MJ, McColl SR, Naccache PH, Cleland LG. Monosodium urate microcrystals induce cyclooxygenase-2 in human monocytes. Blood. 1998;91:1769–1776.

21. Schreiner O, Wandel E, Himmelsbach F, Galle PR, Märker-Hermann E. Reduced secretion of proinflammatory cytokines of monosodium urate crystal-stimulated monocytes in chronic renal failure: an explanation for infrequent gout episodes in chronic renal failure patients? Nephrol Dial Transplant. 2000;15:644–649.

22. Urano W, Yamanaka H, Tsutani H, Nakajima H, Matsuda Y, Taniguchi A,Hara M, Kamatani N. The inflammatory process in the mechanism of decreased serum uric acid concentrations during acute gouty arthritis. J Rheumatol. 2002;29:1950–1953.

Table 1. Comparison of laboratory features of gout with arthritis attack and gout without arthritis attack.

	Gout with arthritis attack (n=45)	***Gout without arthritis attack (n=45)***	***P value***
Hemoglobin, g/dL	13.96±1.50	14.05±1.80	0.961
Platelet, ×10^9/L	260.17±73.22	253.08±76.84	0.880
CRP, mg/L	44.17±50.23	5.56±4.03	<0.0001
ESR, mm/h	29.65±19.40	12.35±9.40	<0.0001
Leukocyte, ×10^9/L	10.12±2.33	8.12±2.14	<0.0001
Neutrophil, ×10^9/L	6.86±2.45	4.49±1.68	<0.0001
Lymphocyte, ×10^9/L	2.17±0.96	2.28±0.97	0.454
Monocyte, x10^9 /L	0.66±0.32	0.49±0.20	<0.0001
NLR, %	4.19±3.37	2.64±1.74	<0.0001
MLR, %	0.36±0.21	0.25±0.15	<0.0001

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NLR: neutrophil to lymphocyte ratio, MLR:monocyte to lymphocyte ratio.

Table 2. Comparison of laboratory features of gout without arthritis attack and controls.

	Gout without arthritis attack (n=45)	*Controls (n=45)*	*P value*
Hemoglobin, g/dL	14.05±1.80	14.91±1.36	0.030
Platelet, ×10^9/L	253.08±76.84	225.65±57.51	0.152
CRP, mg/L	5.56±4.03	3.93±2.71	0.968
ESR, mm/h	12.35±9.40	8.07±6.44	0.309
Leukocyte, ×10^9/L	8.12±2.14	6.68±1.09	0.002
Neutrophil, ×10^9/L	4.49±1.68	3.95±1.07	0.033
Lymphocyte, ×10^9/L	2.28±0.97	2.06±0.46	0.421
Monocyte, x10^9 /L	0.49±0.20	0.44±0.11	0.532
NLR, %	2.64±1.74	2.07±1.01	0.453
MLR, %	0.25±0.15	0.22±0.06	0.604

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio.

Table 3. Correlations between NLR values and CRP, ESR, and leukocyte count.

NLR, %	***CRP***	***ESR***	***Leukocyte***
r_s	0.361	0.193	0.496
p	0.016	0.209	0.001

NLR: neutrophil to lymphocyte ratio, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

Table 4. Correlations between MLR values and CRP, ESR, and leukocyte count.

MLR, %	*CRP*	*ESR*	*Leukocyte*
r_s	0.415	0.236	0.436
p	0.005	0.123	0.003

MLR: monocyte to lymphocyte ratio, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

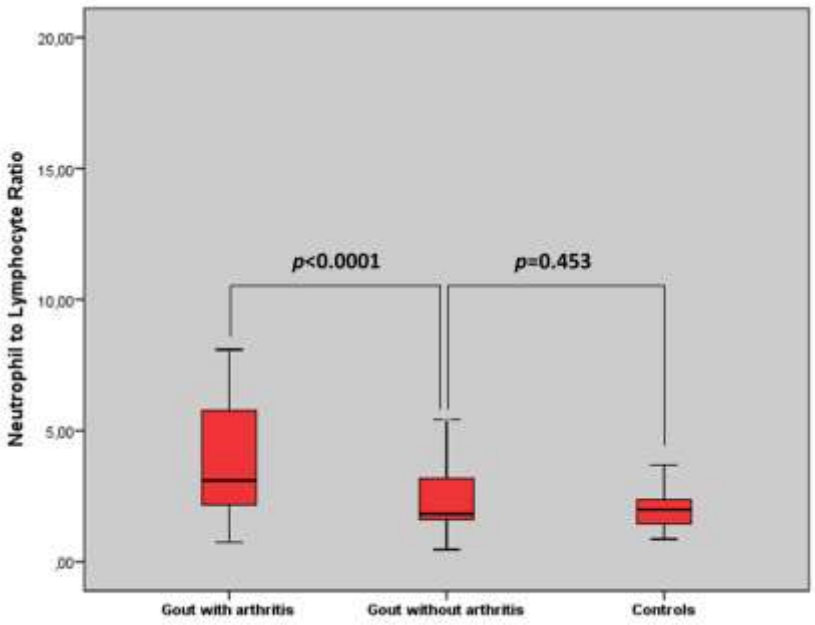

Figure 1. Neutrophil-to-lymphocyte ratio in patients with and without gouty arthritis, and in controls.

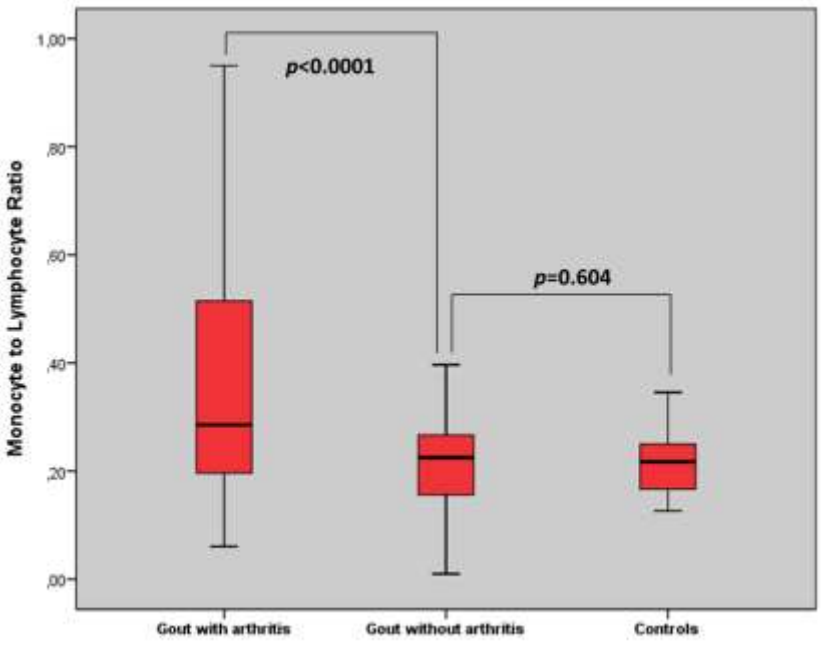

Figure 2. Monocyte-to-lymphocyte ratio in patients with and without gouty arthritis, and in controls.

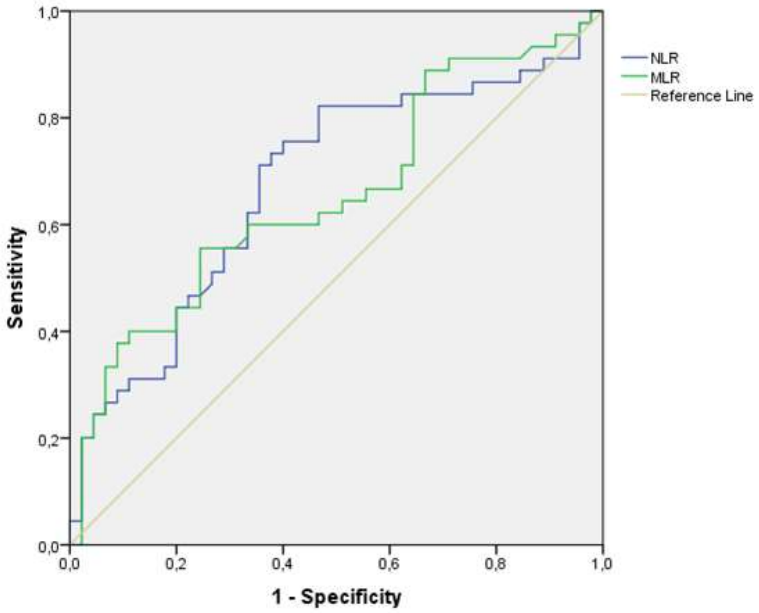

Figure 3. Sensitivity and specificity of NLR and MLR values in gouty arthritis attacks.