ORIGINAL ARTICLE

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

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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: *Neutrophil-to-lymphocyte ratio values were 4.19 ± 3.37 in AGA patients, 2.64 ± 1.74 in patients in remission and 2.07 ± 1.01 in controls. Neutrophil-to-lymphocyte ratio 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). Monocyte-to-lymphocyte ratio values were 0.36 ± 0.21 in AGA patients, 0.25 ± 0.15 in patients in remission and 0.22 ± 0.06 in controls. Monocyte-to-lymphocyte ratio was higher in AGA patients than in 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). The NLR and MLR values in AGA patients had positive correlations with C-reactive protein, erythrocyte sedimentation rate and leucocyte count. The cut-off value of NLR was 2.18 in receiver operating characteristic (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;* $p = 0.011$*).*

Conclusion: *We concluded that MLR and NLR could be used as cheap and useful inflammatory markers predicting arthritis attacks in patients with gout.*

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

INTRODUCTION

Gout disease is an auto-inflammatory disease caused by accumulation of monosodium urate crystals (MSU) in tissues and organs due to hyperuricaemia. 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 hyperuricaemia, detection of MSU without any signs or symptoms, acute gouty arthritis (AGA) and advanced stage gout-chronic tophaceous. Acute gouty arthritis may develop without any organ damage sign after nearly 15–20 years of asymptomatic hyperuricaemia (3–5). Acute gouty arthritis develops due to accumulation of MSU within joints and in adjacent

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tissues, and it has generally a monoarticular presentation. It commonly involves the big toe, ankle and 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 [NLR] and monocyte-to-lymphocyte [MLR] ratio) have been listed in inflammatory markers which have been used more frequently recently. There are many studies performed in 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 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 with AGA and in remission and to determine availability of these markers in clinical practice and as laboratory tests.

SUBJECTS AND METHODS

The present study was performed between May 2014 and February 2015. A total of 45 patients diagnosed with gout disease, and 45 healthy 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 1 hour after the sampling. The complete blood counts were 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, IL, USA) was used for statistical analyses. Continuous variables were presented as mean ± standard deviation, while categorical variables were indicated as number (n) and percent (%). Variables meeting the parametric assumptions were assessed using *t*-test and one-sided analysis of variance test in independent groups, Tukey honestly significant difference test in the intergroup post-hoc evaluation, while categorical variables were reviewed by *chi-square* test. Pearson correlation analysis was used to test the correlation of the data. Receiver operating characteristic (ROC) curve graphics were carried out in the computation of sensitivity and specificity. p values of below 0.05 were accepted as significant.

RESULTS

Of the 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).

Neutrophil-to-lymphocyte ratio 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. Neutrophil-to-lymphocyte ratio value in AGA patients was higher than in patients in remission and 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) (Fig. 1). Monocyte-to-lymphocyte ratio values were 0.36 ± 0.21 in AGA patients, 0.25 ± 0.15 in patients in remission and 0.22 ± 0.06 in controls. Monocyte-to-lymphocyte ratio value in AGA patients was higher than in patients in remission and 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) (Fig. 2). Other laboratory results of AGA patients, patients in remission and control group are summarized in Tables 1 and 2.

Positive correlations were determined between NLR, MLR values and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leucocyte in patients with

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
Haemoglobin, g/dL	13.96 ± 1.50	14.05 ± 1.80	0.961
Platelet, $\times 10^9$/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
Leucocyte, $\times 10^9$/L	10.12 ± 2.33	8.12 ± 2.14	< 0.0001
Neutrophil, $\times 10^9$/L	6.86 ± 2.45	4.49 ± 1.68	< 0.0001
Lymphocyte, $\times 10^9$/L	2.17 ± 0.96	2.28 ± 0.97	0.454
Monocyte, $\times 10^9$ /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
Haemoglobin, g/dL	14.05 ± 1.80	14.91 ± 1.36	0.030
Platelet, $\times 10^9$/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
Leucocyte, $\times 10^9$/L	8.12 ± 2.14	6.68 ± 1.09	0.002
Neutrophil, $\times 10^9$/L	4.49 ± 1.68	3.95 ± 1.07	0.033
Lymphocyte, $\times 10^9$/L	2.28 ± 0.97	2.06 ± 0.46	0.421
Monocyte, $\times 10^9$/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.

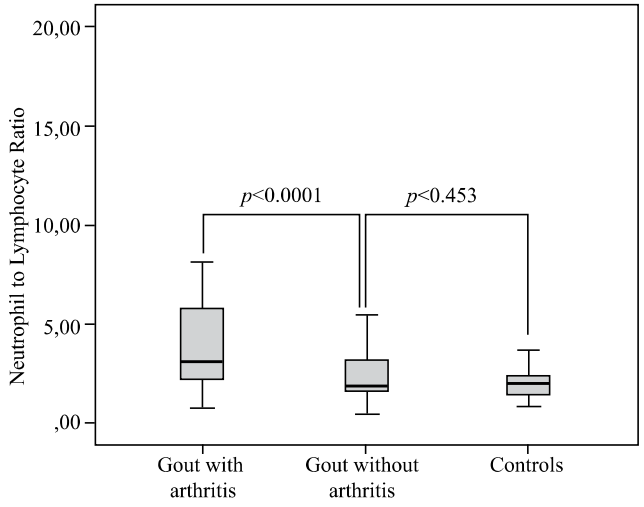

Fig. 1: Neutrophil-to-lymphocyte ratio in patients with and without gouty arthritis, and in controls.

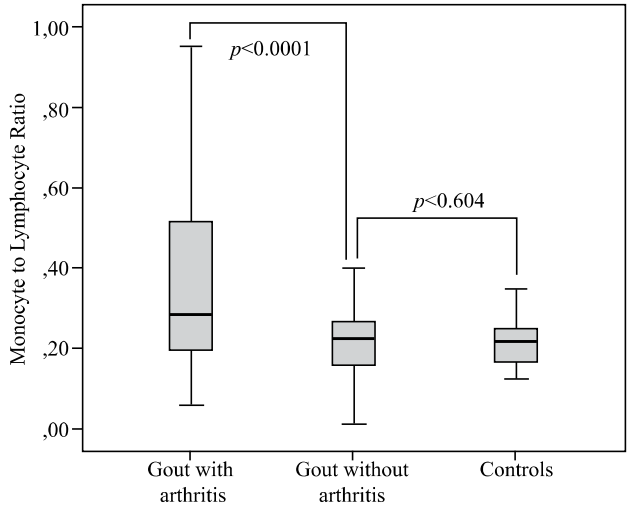

Fig. 2: Monocyte-to-lymphocyte ratio in patients with and without gouty arthritis, and in controls.

Table 3: Correlations between NLR values and CRP, ESR and leucocyte count

NLR, %	CRP	ESR	Leucocyte
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 leucocyte count

MLR, %	CRP	ESR	Leucocyte
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.

AGA (Tables 3 and 4). The cut-off value of NLR was 2.18 in the ROC analysis with sensitivity of 73%, specificity of 63% and AUC of 0.676 (95% Cl 0.542, 0.769, $p = 0.004$) (Fig. 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, $p = 0.011$) (Fig. 3).

DISCUSSION

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

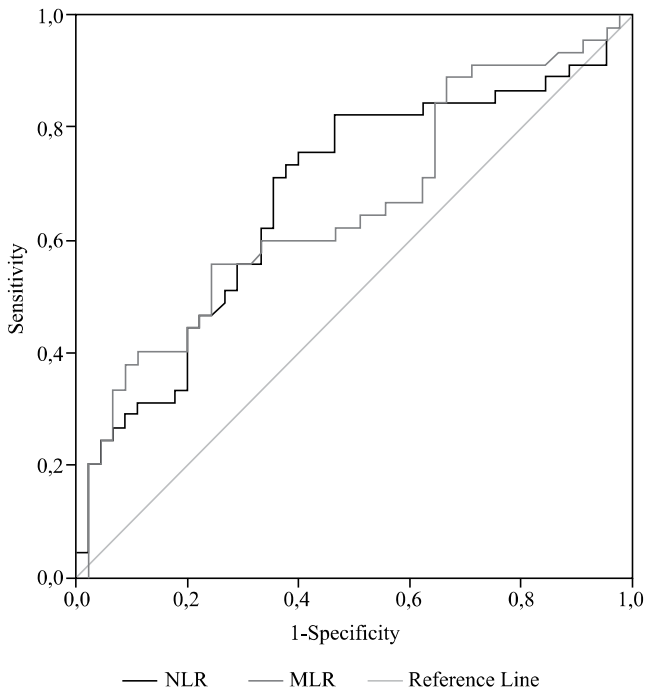

Fig. 3: Sensitivity and specificity of NLR and MLR values in gouty arthritis attacks. MLR = monocyte-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio.

and control group. It was observed that NLR and MLR values were correlated with CRP, ESR and leucocyte 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 function 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. Gökmen *et 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 in 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 patients. 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 to 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 on the immune system may end up with neutrophilia and lymphopenia (15, 20). Urano *et al* (22) showed that cortisol levels in 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. The effects of MSU 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, this suggested a possible correlation with AGA.

The present study has some limitations, which are retrospective study design and low number of enrolled patients. As uric acid levels can be normal in gouty

arthritis attacks, 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 gout patients with arthritis attacks.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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