ORIGINAL ARTICLE

Development of Atherosclerotic Cardiovascular Mortality in Gouty Arthritis and Rheumatoid Arthritis Patients: Are They Associated With Mean Platelet Volume and Neutrophil-Lymphocyte Ratio? A Comparative Study

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ABSTRACT

Objectives: This study aims to evaluate the mean platelet volume (MPV) and neutrophil-lymphocyte ratio (NLR) in gouty arthritis (GA) and rheumatoid arthritis (RA) patients, as well as their relationship with atherosclerotic cardiovascular mortality (ACVM).

Patients and methods: The study included 122 GA patients (96 males, 26 females; mean age 64.6±13.4 years; range 34 to 82 years), 82 RA patients (40 males, 42 females; mean age 62.1±12.1 years; range 29 to 83 years), and 61 healthy controls (34 males, 27 females; mean age 65.3±4.8 years; range 33 to 80 years). Clinical and ACVM data were obtained from medical charts. Erythrocyte sedimentation rate, C-reactive protein, MPV, and NLR were recorded at the time of diagnosis and one month after therapy.

Results: Mean platelet volume in GA (8.49±1.5) and RA (7.98±0.99) groups were significantly lower than in healthy controls (9.8±15) (p<0.001). NLR in healthy controls (1.9±0.74) was significantly lower than in GA (3.6±2.3) and RA (3.7±2.5) groups (p<0.001). After treatment, MPV did not change significantly in GA and RA groups (p values >0.05); however, NLR decreased in both groups (p<0.001). Nine GA and 12 RA patients died from ACVM during follow-up. GA patients with ACVM were older and had more frequent hypertension, higher MPV, and higher intercritical CRP level. In multivariate analysis, MPV was an independent poor prognostic factor for ACVM in GA patients.

Conclusion: Gouty arthritis and RA patients had significantly lower MPV and significantly higher NLR than controls. MPV might be used as a potential biomarker for the development of ACVM in GA.

Keywords: Atherosclerosis; gouty arthritis; mean platelet volume; neutrophil/lymphocyte ratio; rheumatoid arthritis.

Gouty arthritis (GA) is a chronic, inflammatory, and metabolic disease characterized by hyperuricemia.[1] GA has a high mortality and morbidity. Besides possibly causing chronic deformity in joints, it is also associated with renal, metabolic, and cardiovascular disorders.[2] The correlation between GA and atherosclerosis has long been known.[3-5] Despite different opinions, current studies have shown the role of hyperuricemia as an independent factor in increasing the cardiovascular risk.[4] It is known that chronic inflammation predisposes to atherosclerosis in patients with GA, similar to other rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[6-8] There are significant indicators that inflammation during GA triggers proatherogenic and prothrombotic incidents.[9] One recent study has shown that distortion of the balance between the coagulation system and fibrinolysis in patients with GA contributed to the development of atherosclerosis.[10]

Rheumatoid arthritis is a chronic, inflammatory, progressive, and autoimmune disease. Mortality in RA patients is 1.5 times more than the

general population.[11] Pathophysiology of cardiovascular diseases in RA could be explained by early atherosclerosis triggered by inflammation. Nowadays, atherosclerosis is considered an autoimmune disease. The presence of immune cells, such as macrophages and active lymphocytes, within the atherosclerotic plaque is a strong indication for involvement of immune system.[6,12,13]

Mean platelet volume (MPV) measured during the routine blood count reflects the size of platelets. It is presumed that MPV -which is considered an important sign of platelet activation- plays a crucial role in the pathophysiology of atherosclerosis.[14,15] Studies reported some association between increased MPV levels and acute, chronic cerebrovascular incidents.[16] The importance of MPV as a marker of inflammation in chronic inflammatory diseases, such as ankylosing spondylitis and RA, was also reported.[17] To our knowledge, whether MPV can be used as an indicator of inflammation in GA and its relationship to atherosclerosis has not been investigated until now.

Neutrophil-lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and regarded as a sign of inflammation. A relationship between high NLR and increased atherosclerotic cardiovascular mortality (ACVM) was reported.[18] In addition, NLR was stated to be an indicator of inflammation in several diseases such as familial Mediterranean fever, SLE, cardiovascular diseases, and malignancies.[18-21] However, to our knowledge, the relationship between NLR and GA -as well as RA- and its role in increased atherosclerosis in these diseases have not been studied yet. Therefore, in this study, we aimed to evaluate the MPV and NLR in GA and RA patients, as well as their relationship with ACVM.

PATIENTS AND METHODS

We retrospectively examined the files of 122 patients with GA (96 males, 26 females; mean age 64.6±13.4 years; range 34 to 82 years) and 82 patients with RA (40 males, 42 females; mean age 62.1±12.1 years; range 29 to 83 years) who were treated between January 2006 and December 2014 in the center, Department of Rheumatology. Acute GA was diagnosed according to the 1977 preliminary classification criteria of American Rheumatism Association,[22] and RA was diagnosed according to the 1987 classification criteria of the American College of Rheumatology.[23] Except for GA, this study did not include patients with rheumatologic inflammatory diseases, malignancy, or active infections. We also included 61 healthy individuals (34 males, 27 females; mean age 65.3±4.8 years; range 33 to 80 years) who had no chronic diseases, were nonsmokers, and were not using any drugs, abused substances or alcohol as the control group. We recorded all parameters in the whole blood count including MPV, platelet distribution width, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and uric acid levels at the initial presentation in GA and RA patients; and after one month of treatment. The same parameters were also studied in healthy control individuals. We obtained permission for the study protocol from the Trakya University Medical Faculty Ethics Committee. We assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. A written informed consent was obtained from each patient.

We recorded overall survival, history of atherosclerosis, and causes of mortality for GA and RA patients. Patients who did not show up for treatment were given phone calls to check whether they had any atherosclerotic cardiovascular incidents. The causes of mortality for patients who died were also recorded. We excluded patients who died because of causes other than atherosclerotic cardiovascular incidents. Our study also included levels of triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, presence of diabetes mellitus, hypertension, and use of alcohol and tobacco as risk factors for ACVM.

In our study, some parameters in whole blood count (hemoglobin, leukocytes, neutrophils, lymphocytes, hemoglobin, MPV, and platelet distribution width) were recorded (PocH-100i, Sysmex, Hamburg, Germany). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. ESR was also recorded (VacuPlus ESR-120,

Eventus Med, Turkey). CRP level was determined from serum (BN II System, Siemens, Liederbach, Germany) with the nephelometry technique. Lipid profiles of all the participants (triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein) and uric acid level were analyzed (Architect c16000, Abbott, USA) from serum, which was obtained from blood samples by centrifugation for five minutes at 4000 rpm. All the laboratory parameters were determined with the same method and devices during the entire period of our research.

Statistical analysis

In comparing categorical data sets, the chi-square test and, as necessary, Fisher's exact test were used. In comparing continuous variables of the groups, analysis of one-way variance and post-hoc Tukey tests were used. For correlation analysis, the Pearson's correlation test was used.

RESULTS

Male sex, hypertension, and alcohol usage were significantly more frequent in GA group compared to RA group (all p values <0.001). Other clinical and biochemical parameters are shown in Table 1.

Mean platelet volume in GA and RA groups were significantly lower than in healthy controls (all p values <0.001). In GA group, MPV was significantly higher than in RA group (p=0.027). NLR in healthy controls was significantly lower than in GA and RA groups (all p values <0.001). ESR and CRP values in GA and RA groups were significantly higher than in controls.

Data prior to and after treatment were available for analysis in 118 GA and 78 RA patients. After treatment, ESR, CRP, platelet count, and NLR level decreased significantly in GA and RA groups (p values <0.001), while MPV level did not change significantly (Table 2).

In GA patients, MPV had a weak positive correlation with uric acid level (r=0.21, p=0.05) and a negative correlation with low-density lipoprotein level (r=0.23, p=0.043). NLR had a weak positive correlation with ESR (r=0.22, p=0.043) and a negative correlation with triglyceride level (r=-24, p=0.019). In RA patients, NLR level correlated with CRP level (r=0.34, p=0.002).

Within a median of 105 months of follow-up (range: 8 to 180 months), nine patients with GA (seven males and two females) died because of ACVM. In univariate analysis, female sex was a poor prognostic factor (median 96 months vs 108 months, p=0.05). In addition, GA patients with ACVM had a higher mean age (76.6±11.1 years vs 63.7±13.2 years, p=0.005), more frequent hypertension (100% vs 53.6%, p=0.01), higher MPV (9.65±1.59 vs 8.39±1.47, p=0.015), and increased intercritical CRP level (1.9±2.4 vs 0.28±0.2, p=0.05). In multivariate analysis, the only independent poor prognostic factor for ACVM was the initial MPV value (OR: 9.3, 95% confidence interval: 1.26-69.1, p=0.0029) in GA patients.

Within a median of 84 months of follow-up (range: 9 to 184 months), 12 RA patients (9 males and 3 females) died because of ACVM. In univariate analysis, male sex was a poor prognostic factor (median 96 months vs 108 months, p=0.05). RA patients with ACVM had significantly more frequent hypertension (58.3% vs 22.9%, p=0.031), older age (73.1±9.8 years vs 60.2±12.5 years, p=0.001), higher platelet count (254±84.3 vs 350.5±93.9, p=0.001) and higher uric acid (6.2±0.7 vs 4.8±1.3, p=0.026) and NLR (6.22±4.7 vs 3.3±1.6, p=0.05). Multivariate analysis in RA group revealed that male sex (odds ratio: 8.7, 95% confidence interval: 1.4-52.6, p=0.019) and older age (odds ratio: 1.09, 95% confidence interval: 1.01-1.17, p=0.022) were independent risk factors for ACVM.

DISCUSSION

To the best of our knowledge, our research is the first study demonstrating MPV as a poor prognostic factor for ACVM in patients with GA based on results from both univariate and multivariate analyses. This study showed that MPV was significantly lower in GA and RA patients with respect to healthy controls. In addition, NLR was seen to be a risk factor in RA patients in univariate analysis. In addition, NLR was higher in patients with acute GA and active RA than in healthy controls; and NLR was observed to normalize after treatment. Our study, to our knowledge, is unique for revealing that NLR may be a useful biological marker in

Table 1. Clinical and laboratory features of patients with gouty arthritis and rheumatoid arthritis

	Gouty arthritis			Rheumatoid arthritis			Controls		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Sex									
Male	96			40			34		
Female	26			42			27		
Age (years)			64.6±13.4			62.1±12.9			65.3±4.8
Diabetes mellitus	15	12.3		12	14.6				
Hypertension	70	57.4		23	28				
Hyperlipidemia	20	16.4		9	11				
Smoking	33	27		19	23.2				
Alcohol	30	24.6		3	3.7				
Ischemic heart disease	18	14.8		11	13.4				
Cerebrovascular disease	6	4.9		3	3.7				
ESR (mm/hr)			57.0±29.8			58±27.1			14.0±9.2
CRP (mg/dL)			9.5±19.3			4.7±5.1			0.3±0.1
Uric acid (mg/dL)			7.9±2.1			5.0±1.3			5.4±1.6
Triglycerides (mg/dL)			165±10			116±7			-
Total cholesterol (mg/dL)			181±5			176±5			-
HDL (mg/dL)			42±2			46±2			-
LDL (mg/dL)			117±4			116±6			-
Hemoglobin (g/dL)			13.3±0.2			12.3±0.2			13.9±1.2
Leukocytes (x10³/mm³)			10.0±0.3			9.70±0.4			6.98±1.37
Neutrophils (x10³/mm³)			6.8±3.3			6.7±3.0			4.0±1.1
Lymphocytes (x10³/mm³)			2.1±0.8			2.1±0.8			2.0±0.7
Neutrophil/lymphocyte ratio			3.7±2.3			3.7±2.5			1.9± 0.7
Platelets (x10³/mm³)			294.6±107			336.4±98.3			248.3±61.7
PDW (fL)			20.7±11.5			19.4±8.8			15.8±7.2
MPV (fL)			8.5±1.5			8.0±1.0			9.8±1.5

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PDW: Platelet distribution width; MPV: Mean platelet volume.

evaluating acute inflammation and response to treatment in GA.

In addition to the platelet count, the most frequent test to evaluate platelets is the MPV. Previous studies showed that MPV correlated with platelet function and activation, and larger thrombocytes behaved more actively when compared to smaller platelets.[24] Studies recently showed the correlation between MPV and inflammatory diseases.[16,17] Moreover, it was suggested that higher MPV was a risk factor for acute myocardial infarction and stroke; and

Table 2. Erythrocyte sedimentation rate, C-reactive protein, platelet count and neutrophil-lymphocyte ratio levels before and after one month of treatment in gouty arthritis and rheumatoid arthritis groups (p values <0.001)

	Gouty arthritis			Rheumatoid arthritis		
	Before treatment	After treatment		Before treatment	After treatment	
	Mean±SD	Mean±SD	p	Mean±SD	Mean±SD	p
ESR	52.7±27.6	15.4±12.6	<0.001	57.3±26.8	21.9±13.0	<0.001
CRP	8.5±11.0	0.5±0.5	<0.001	4.6±5.01	0.6±0.4	<0.001
MPV	8.4±1.6	8.6±1.2	0.423	8.0±0.9	8.1±0.9	0.547
NLR	3.7±2.4	2.3±1.5	<0.001	3.7±2.5	2.5±1.1	<0.001
Platelets	288.0±10.4	239.2±6.6	<0.001	337.3±11.2	275.6±7.5	<0.001

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil-lymphocyte ratio.

may be useful in predicting these events.[16] It was shown that an increased MPV may be an indicator of macrovascular and microvascular disease in patients with scleroderma.[25]

Another study revealed that MPV in patients with inflammatory diseases, such as AS and RA, was considerably lower than in healthy controls. It also reported that MPV normalized after treatment and may be used as a sign of activation in these diseases.[17] In our study, similarly, we determined that patients with acute GA and RA had considerably lower MPV compared to healthy controls.

The clinical use of NLR in different diseases has been discussed in several studies. A study showed that NLR in patients with acute coronary syndrome was significantly higher than in patients with stable angina pectoris and coronary artery atherosclerosis. A significant relationship was also reported between the intensity of coronary artery disease and NLR.[18] NLR in patients with SLE and psoriasis was observed to be significantly higher than in healthy controls.[20,26] While we observed that the NLR in GA patients at diagnosis was higher than in healthy controls, we also noted that the NLR decreased significantly one month after treatment compared to pretreatment values. With this study, we can propose that NLR may be an important biomarker for estimating the response to inflammation in acute attacks of GA.

Many studies were performed to explain the relationship between GA and atherosclerosis. Some proposed that hyperuricemia was

an independent cardiovascular risk factor as diabetes mellitus, hypertension, and obesity.[4] A study determined that carotid intima-media thickness was markedly increased in patients with GA in comparison to patients with RA and asymptomatic hyperuricemia. It was also emphasized that hyperuricemia and inflammation in patients with GA might have cumulative effects on the development of atherosclerosis.[17]

In this study, we determined that female sex was a poor prognostic factor for ACVM in patients with GA in univariate analysis. In addition, we observed that the average age, frequency of hypertension, CRP, and MPV values were higher in GA patients with ACVM.

The risk of mortality in RA patients is higher than the general population, and highly correlated with cardiovascular diseases.[11] It was shown that systemic inflammation and proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interleukin-17) contributed to increased atherosclerosis in RA.[13] Our study found that male sex was a poor prognostic factor for ACVM in patients with RA. Also, the frequency of hypertension, mean age, mean platelet count, uric acid level, and NLR were associated with ACVM in univariate analysis. In multivariate analysis, we observed that male sex and age were independent risk factors in RA patients. Our research is valuable since, to our knowledge, it is the first study demonstrating NLR as a risk factor for ACVM in patients with RA.

One of the limitations of this study was that the sex distribution of GA and RA patients were not similar. In fact, this is a natural result of the diseases, since GA is more prevalent among males, while RA is more common among females. Our main purpose was to evaluate MPV and NLR in patients with GA and also determine their relationship with ACVM. The reason we focused on patients with RA was to follow the progression of MPV and NLR in another chronic inflammatory disease. Therefore, we included patients with RA as the positive control group in this study. Also, the presence of obesity which is a risk factor for ACVM was not taken into consideration in our study.

In conclusion, in GA patients, the frequency of ACVM was very similar to that in RA patients. NLR values decreased after treatment in both GA and RA groups. MPV level was a poor prognostic biomarker for ACVM in GA patients in both univariate and multivariate analysis. In addition, NLR was a risk factor for ACVM in RA.

Declaration of conflicting interests

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