Can Hematologic Parameters be an Indicator of Metabolic Disorders Accompanying Rosacea?

Asli Akin Belli[1], ***Asude Kara***[1], ***Seyran Ozbas Gok***[2]

[1]Mugla Sitki Kocman University Training and Research Hospital, Department of Dermatology, Mugla, Turkey; [2]Artvin Hopa State Hospital, Department of Dermatology, Artvin, Turkey

Corresponding author:
Asli Akin Belli, MD
Mugla Sitki Kocman University,
Department of Dermatology
48000, Mugla
Turkey
dr_asliakin@hotmail.com

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ABSTRACT Recently, diverse hematologic parameters have been used as an indicator of the presence or severity of inflammatory and cardiovascular diseases. Our aim was to investigate the ratios of neutrophils to lymphocytes (NL), monocytes to high-density lipoprotein (HDL) cholesterol (MHC), and platelets to lymphocytes (PL) in patients with rosacea in comparison with the control group and determine whether there was a correlation between these ratios and metabolic disorders in patients with rosacea. We conducted a case-control study on 61 patients with rosacea and 60 healthy controls between January 2015 and January 2016 at the Dermatology Outpatient Clinic, Mugla, Turkey. Demographic data, biochemical parameters, hematologic parameters and ratios, the presence of metabolic syndrome (MS), and the presence of insulin resistance (IR) in the participants were recorded. Sixty one patients with rosacea (16 men, 45 women) and 60 controls (13 men, 47 women) were included in the study. The NL ratio, mean levels of low-density lipoprotein (LDL) and total cholesterol, triglyceride, C-reactive protein (CRP), systolic and diastolic blood pressures, and the presence of IR were significantly higher in patients with rosacea than in controls. In the rosacea group, the MHC ratio was significantly higher in patients with rosacea with IR and MS. Moreover, only the MHC ratio was an independent predictor of MS according to univariate logistic regression analysis. The cutoff value of MHC on admission for predicting MS in patients with rosacea was 0.013.The higher levels of NL ratio and IR in the rosacea group corroborate the previous studies demonstrating a high level of cardiovascular risk factors in patients with rosacea. The MHC ratio may be used as a simple and inexpensive method to predict metabolic disorders in patients with rosacea.

KEY WORDS: hematologic parameters, insulin resistance, metabolic syndrome, rosacea

INTRODUCTION

Various hematologic parameters or ratios have recently been used as an indicator of the presence or severity of inflammatory diseases. Insulin resistance, coronary artery disease, hypertension, and inflammatory skin diseases such as psoriasis and Behçet's disease have been evaluated (1-5). Rosacea is also a chronic inflammatory skin disease (6). It has been proposed that inflammation related to the excessive response of the innate immune system by various triggers plays a key role in the pathogenesis of rosacea (7-11). In recent studies, dyslipidemia, hypertension, and cardiovascular risk factors have been reported to be high in patients with rosacea (6,12,13). Furthermore, there was a very recent report on the increased frequency of insulin resistance and some parameters of metabolic syndrome in patients with rosacea (14).

To the best of our knowledge, there is no study investigating the hematological ratios in patients with rosacea or the relationship between these ratios and metabolic disorders accompanying rosacea.

Our aim was to investigate the neutrophil-to-lymphocyte (NL), monocyte-to-high-density lipoprotein (HDL) cholesterol (MHC), and platelet-to-lymphocyte (PL) ratios in patients with rosacea in comparison with the control group and determine whether there was a correlation between these ratios and metabolic syndrome and insulin resistance in patients with rosacea.

METHODS

We conducted a case-control study on 61 patients with rosacea and 60 healthy controls (matched for age, sex, and body mass index) between January 2015 and January 2016 at the Dermatology Outpatient Clinics of the Mugla Sitki Kocman University Training and Research Hospital. Ethic Committee approval was obtained before the study from the local hospital Ethic Committee. The diagnosis of rosacea was based on characteristic clinical findings according to the National Rosacea Society criteria. The controls were selected randomly from the patients who were admitted to the outpatient clinic with various skin problems other than rosacea. Inclusion criteria for the participants were absence of known diabetes mellitus, coronary artery disease, hyperlipidemia, and chronic inflammatory disease (including inflammatory skin diseases).

Age, sex, body mass index (BMI), lipid profile (total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein), fasting blood glucose (FBG), insulin, C-reactive protein (CRP), the ratios of NL, MHC, and PL (obtained from the complete blood count), systolic and diastolic blood pressure levels, and the presence of metabolic syndrome (MS) and insulin resistance (IR) were recorded.

BMI was calculated using the formula weight (kg) / height (m^2). Lipid parameters, insulin, and FBG levels were studied after a 12-hour fasting period. Based on the diagnostic criteria of the International Diabetes Federation (IDF-2005), MS was defined as waist circumference >94cm in men and >80cm in women plus at least two of the following criteria: triglyceride value >150 mg/dL or specific treatment for this lipid abnormality, high density lipoprotein; <40 mg/dL in

Table 1. Comparison of the demographic, biochemical, metabolic, and hematologic parameters in the rosacea and control groups

	Rosacea group n (%) or mean ± SD	**Control group n (%) or mean ±S D**	***P***
Women **Men**	45 (73.8) 16 (26.2)	47 (78.3) 13 (21.7)	0.557
Age	50.46±8.58	49.80±9.70	0.693
BMI (kg/m²)	28.19±3.76	27.18±3.36	0.123
LDL (mg/dL)	129.87±31.46	119±26.39	**0.042**
HDL (mg/dL)	57.19±14.51	57.62±16.69	0.938
T. cholesterol (mg/dL)	214±35.47	199.76±34.89	**0.028**
Triglyceride (mg/dL)	83.09±8.79	76.04±9.39	**0.036**
FBG (mg/dL)	96.42±14.53	91.83±7.36	0.128
Systolic BP (mmHg)	126.80±16.71	118.50±14.12	**0.004**
Diastolic BP (mmHg)	82.29±9.20	75.83±9.26	**<0.001**
Presence of IR	22 (36.1)	11 (18.3)	**0.029**
Presence of MS	21 (34.4)	13 (21.6)	0.118
CRP (mg/dL)	3.33±3.11	2.26±2.22	**0.016**
Neutrophil count (K/mL)	2.19±0.99	1.75±0.62	0.088
Lymphocyte count (K/mL)	1.97±0.63	2.05±0.55	0.455
Platelet count (K/mL)	244.21±57.87	258.96±66.35	0.195
Monocyte count (K/mL)	0.39±0.12	0.35±0.16	0.106
NL ratio	2.11±0.97	1.73±0.64	**0.012**
MPV ratio	9.29±1.01	9.61±1.21	0.115
MHC ratio	0.0073±0.0030	0.0067±0.0047	0.447
PL ratio	132.73±45.06	131.58±36.58	0.880

Chi-square test, Student's t-test, and Mann-Whitney U test. BMI: body mass index; FBG: fasting blood glucose; BP: blood pressure; IR: insulin resistance; MS: metabolic syndrome; CRP: C-reactive protein; NL: neutrophil/lymphocyte; MHC: monocyte/high-density lipoprotein (HDL) cholesterol; LDL: high-density lipoprotein; PL: platelet/lymphocyte; MPV: mean platelet volume; SD: Standard Deviation

Table 2. Comparison of hematologic parameters in patients with or without IR and MS

	IR (+) n=22 Mean ± SD	IR (-) n=39 Mean ± SD	*P*	MS (+) n=21 Mean ± SD	MS (-) n=40 Mean ± SD	*P*
NL ratio	2.15±1.04	2.08±0.95	0.088	2.39±1.09	1.96±0.89	0.088
MHC ratio	0.0080±0.0034	0.0069±0.0027	**0.008**	0.0087±0.0031	0.0066±0.0027	**0.007**
PL ratio	140.43±54.44	128.39±38.92	0.505	138.11±59.73	129.92±35.65	0.505
Neutrophil count (K/mL)	3.74±0.90	3.88±1.59	0.448	2.39±1.09	1.96±0.89	0.088
Lymphocyte count (K/mL)	2.01±0.85	1.95±0.47	0.387	1.87±0.88	2.02±0.45	0.387
Platelet count (K/mL)	252.32±62.16	239.64±55.62	0.084	226.52±54.19	253.50±58.22	0.084
MPV (fl)	9.03±0.99	9.44±1.01	0.376	9.45±1.01	9.21±1.02	0.376
Monocyte count (K/mL)	0.39±0.12	0.39±0.12	0.840	0.40±0.11	0.39±0.13	0.840

Student's t-test and Mann-Whitney U test. IR: insulin resistance; MS: metabolic syndrome; NL: neutrophil/lymphocyte; MHC: monocyte/ high-density lipoprotein (HDL) cholesterol; PL: platelet/lymphocyte; MPV: mean platelet volume; SD: Standard Deviation

men and <50 mg/dL in women or specific treatment for this lipid abnormality, blood pressure ≥130/85 mmHg or antihypertensive treatment, and fasting blood glucose ≥100 mg/dL or diagnosed diabetes mellitus (15).

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula: [fasting insulin level (uIU/mL) × fasting glucose level (mg/dL)/405]. A value of >2.7 was considered to indicate IR.

For the data analysis, the statistical program "SPSS for windows 20.0" was used. The chi-square test was used for the analysis of qualitative data. The distribution of variables was checked with the Kolmogorov-Smirnov test. The Student's t-test and Mann-Whitney U-test were used for variables with normal and abnormal distribution, respectively. *P*<0.05 was considered significant.

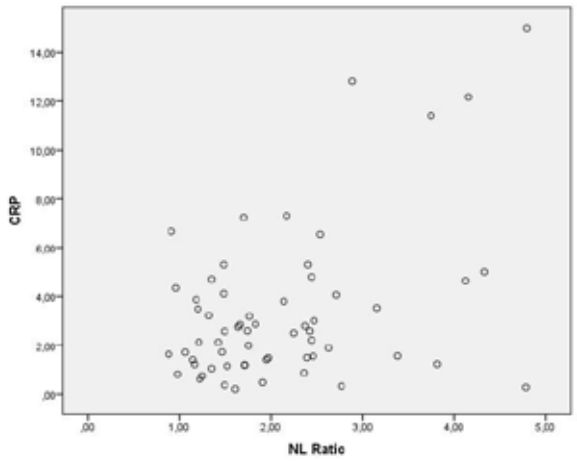

Figure 1. Correlation between the neutrophil–to-lymphocyte (NL) ratio and C-reactive protein (CRP) levels in patients with rosacea.

RESULTS

Sixty one rosacea patients (16 men, 45 women; age range 35-74 years) and 60 healthy controls (13 men, 47 women; age range 33-78 years) were included in the study. The duration of the disease varied between 3 months to 20 years (mean ± Standard Deviation:

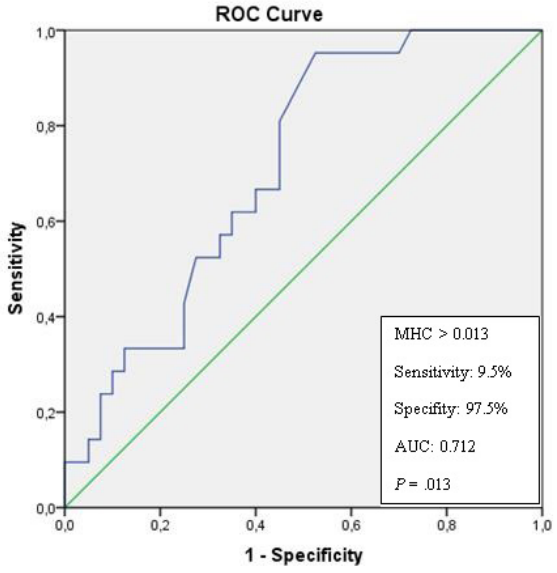

Figure 2. Receiver operating the characteristics curve of monocyte count to high-density lipoprotein (HDL) cholesterol (MHC) ratio for predicting metabolic syndrome in patients with rosacea (AUC: Area under the curve)

1.75±3.53 years) in patients with rosacea. Of the patients, 29 (47.5%) had the erythematotelangiectatic type of rosacea, while 31 (50.8%) had papulopustular type and one (1.6%) had the phymatous type.

Among the hematological ratios, the NL ratio of the rosacea group was significantly higher than in the control group (P=0.012). The NL ratio levels were correlated with CRP levels (P<0.05) **(**Figure 1**)**. Other than the NL ratio, the mean levels of LDL, total cholesterol, triglyceride, CRP, systolic and diastolic blood pressures, and presence of IR were significantly higher in patients with rosacea than those of controls (P<0.05) (Table 1).

When we evaluated only the rosacea group, the MHC ratio was significantly higher in the patients with MS and IR (P=0.007 and P=0.008, respectively) (Table 2). There was no correlation between rosacea subtype and hematological ratios (P>0.05). In addition, only the MHC ratio was an independent predictor of MS in the rosacea group, according to univariate logistic regression analysis (P=0.015, OR: 1.54, CI: 1.723-1.371). The cutoff value of the MHC ratio on admission for predicting MS in patients with rosacea was 0.013 with 9.5% sensitivity and 97.5% specificity (area under the curve 0.712, P=0.013) (Figure 2).

DISCUSSION

Diverse hematologic ratios have recently become popular for predicting the course of cardiovascular diseases, various cancers, and inflammatory diseases. Since rosacea is an inflammatory disease with a known association with cardiovascular diseases, we conducted the current study to determine whether the hematological ratios may be used to predict metabolic disorders accompanying rosacea. We found that the NL ratio of patients with rosacea was significantly higher than that of controls, and that the MHC ratio significantly higher in patients with rosacea with MS and IR.

Although the pathogenesis of rosacea has not been completely elucidated, increased levels of cathelicidin peptides (LL-37), kallikrein-5 (KLK5), toll-like receptor 2 (TLR2), endoplasmic reticulum (ER) stress, oxidative stress, and pro-inflammatory cytokines (TNF-α, IL-8, and IL-1β) have been found in rosacea-effected skin (7-11). Similar pathogenetic mechanisms such as ER stress, oxidative stress, high LL-37 levels, and high inflammatory cytokines have been demonstrated in the development of atherosclerosis, MS, and cardiovascular diseases (16-19). Although Egeberg *et al.* did not find an association between rosacea and increased risk of adverse cardiovascular outcomes or death, an association between rosacea to cardiovascular diseases, MS, and IR have been reported in some studies (6,12-14,20).

Similarly to rosacea, psoriasis and Behçet's disease are chronic inflammatory skin diseases which are associated with metabolic syndrome and cardiovascular diseases. Moreover, psoriasis and Behcet's disease are also systemic diseases, which is not the case with rosacea. The hematologic ratios have been used in psoriasis and Behcet's disease to determine underlying inflammation or cardiovascular risk factors. Yurtdas *et al.* found that the NL ratio was significantly higher and the only predictor of subclinical atherosclerosis in patients with psoriasis (4). Sen *et al.* have reported similar high NL ratios in patients with psoriasis and a positive correlation between the NL ratio and CRP levels (21). Furthermore, both the NL and PL ratios have been noted as strong predictors of psoriatic arthritis in a study involving patients with psoriasis, psoriatic arthritis, and healthy controls (22). In another two studies, the NL ratio and carotid intima media thickness have been found to be high in patients with Behçet's disease (23,24). These results corroborate the hypothesis that inflammation and endothelial dysfunction have an important role in the pathogenesis of Behçet's disease, and that NL ratio may be used to evaluate the disease activity. Additionally, Rifaioglu *et al.* noticed that the NL ratio was significantly increased in patients with active Behçet's disease (5). Alan *et al.* have suggested that NL ratio may be a diagnostic criterion of Behçet's disease based on the results of their study (25).

The hematologic ratios, particularly NL and MHC ratios, were first used for cardiovascular diseases, metabolic disorders, and some cancers. Several studies showed that NL ratio is an inexpensive and easy indicator of atherosclerosis, hypertension, and inflammation (2,3). Furthermore, Lou *et al.* noticed that the NL ratio and IR were significantly associated (1). Buyukkaya *et al.* also found a relationship between NL ratio and MS, as well as severity of MS. In a cross-sectional study consisting of 1070 individuals, increased NL ratio levels were significantly related to chronic diseases such as hypertension and diabetes mellitus (26). It has been proposed that neutrophils increase damage to the endothelium by interacting with endothelial tissue and that they play a key role in the development of inflammation, and thus atherosclerosis (2).

MHC ratio has been found to be high in patients with slow coronary flow, as reported by Canpolat et al (27). In another study, 340 patients with chronic renal disease were followed for about 33 months, finding that cardiovascular events were more common in

patients with high MHC ratio (28). Monocytes interact with damaged endothelium and induce over-expression of pro-inflammatory cytokines and adhesion molecules. Contrarily, HDL cholesterol has anti-inflammatory, anti-oxidant, and vasodilator effects (27). Thus, MHC ratio has been considered a good indicator of inflammatory conditions such as cardiovascular events. In order to provide a fair comparison, since a relationship between these hematological ratios and obesity has been previously reported, our study included BMI-matched subjects in the rosacea and control groups. When the rosacea and control groups were compared, the NL ratios of the rosacea group were significantly higher than those of control group. However, only MHC ratio was an independent predictor of MS in patients with rosacea.

CONCLUSION

The presence of high cardiovascular risk factors among patients with rosacea in recent studies encouraged us to perform the current study. The higher levels of NL ratio and IR we found in the rosacea group corroborate the previous studies, demonstrating the presence of high cardiovascular risk factors in patients with rosacea. In the rosacea group, MHC ratio was significantly higher in patients with MS and IR. MHC ratio may be used as a simple and inexpensive method to indicate metabolic disorders accompanying rosacea. Further studies are needed to duplicate our results and to evaluate the usefulness of hematologic parameters for predicting metabolic disorders in rosacea.

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