

# Metabolic syndrome, hematological markers of inflammation and disease activity in rheumatoid arthritis

**Background:** The coexistence of Rheumatoid Arthritis (RA) and Metabolic Syndrome (MetS) is common.

**Aim:** The present study assessed the effect of MetS on disease activity and hematological markers of inflammation to Platelets/Lymphocyte Ratio (PLR) and Neutrophil/Lymphocyte Ratio (NLR) in RA patients.

**Study design:** A cross-sectional case control study using STARD reporting guideline.

**Methods:** The present study included 5 groups: treatment-naïve RA patients with MetS (GI, n=50), treated RA patients with MetS (GII, n=50), treatment-naïve RA patients without MetS (GIII, n=50), treated RA patients without MetS (GIV, n=50) and healthy age and sex-matched controls (GV, n=50). RA was diagnosed based on the 2010 ACR/EULAR criteria. Disease activity of RA patients was calculated using the DAS-28 score. For the diagnosis of MetS, we adopted the Harmonized Joint Scientific Statement (HJSS) on metabolic syndrome recommendations.

**Results:** Patients in GI had significantly higher DAS28 when compared with other groups. GII and GIII patients had significantly higher DAS28 when compared with GIV. It was also shown that GI patients had significantly higher PLR and NLR when compared with GIII. Similarly, GII patients had significantly higher PLR and NLR when compared with GIV. Logistic regression analysis identified presence only MetS [OR (95%CI): 8.66 (1.34-56.1), p=0.024] and increased PLR (OR (95%CI): 0.98 (0.96-0.99), p=0.002) as independent predictors of high disease activity in treatment-naïve patients while increased PLR was the only independent predictor of disease activity in treatment-experienced patients.

**Conclusion:** Metabolic syndrome is associated with elevated hematological markers of inflammation and disease activity in treatment-naïve RA patients. Both PLR and NLR are risk factors for RA activity in treatment-naïve patients with PLR being more strongly correlated with disease activity.

**Keywords:** rheumatoid arthritis • metabolic syndrome • platelets/lymphocyte ratio • neutrophil/lymphocyte ratio

## Key points

- Rheumatoid arthritis and metabolic syndrome commonly coexist.
- Coexistence of both conditions is associated with increased inflammatory activity.
- This can be expressed as increased PLR and NLR.
- Increased PLR and/or NLR are associated with increased disease activity.

## Introduction

Rheumatoid Arthritis (RA) is a chronic disease that primarily affects joints. It is characterized by a profound inflammatory state and

autoimmune nature [1]. The recent years have witnessed increasing global disease incidence and prevalence with evidently associated morbidity and mortality [2]. The risk of

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developing RA combines genetic and environmental factors including age, low physical activity, and increased body weight [3]. Moreover, many studies recognized a significant relation between RA and Metabolic Syndrome (MetS). In fact, many components of MetS e.g. obesity and dyslipidemia are frequently seen in RA patients [4]. While the prevalence of MetS in RA patients showed wide variation among different studies [5], the confounding of MetS in RA patients was associated with more disease activity [6,7].

The inter-relation between RA and MetS is probably attributed to the underlying inflammatory state they share in common [8]. It is understood that innate and adaptive immune cells play an essential role in the production and enhancement of the chronic inflammatory state associated with RA [9]. Also, MetS is regarded as an inflammatory disorder in which inflammatory pathways are implicated in the disease pathogenesis [10].

Besides the traditional inflammatory markers, new hematological markers of inflammation including Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) were linked to RA [11] and MetS [12,13]. However, no studies assessed how the coexistence of RA and MetS can affect the levels of these markers.

The present study aimed to evaluate the inflammatory state in patients with co-existing RA and MetS as expressed by the hematological markers NLR and PLR.

#### Subjects and methods

The present study is a cross-sectional case-control study. The study protocol was approved by the local ethical committee and all participants gave informed consent before enrollment.

The present study included 5 groups: treatment-naïve RA patients with MetS (GI, n=50), treated RA patients with MetS (GII, n=50), treatment-naïve RA patients without MetS (GIII, n=50), treated RA patients without MetS (GIV, n=50) and healthy age and sex-matched controls (GV, n=50). Patients were included in the present study if they were diagnosed with RA or MetS while receiving RA treatment or not according to the study group. Patients were excluded if they had associated diabetes mellitus, autoimmune or allergic diseases, known infections or malignant tumors.

Upon recruitment, all participants were submitted to careful history taking, thorough clinical examination and standard laboratory investigations. RA was diagnosed

based on the 2010 ACR/EULAR criteria [14]. Disease activity of RA patients was calculated using the DAS-28 score. The score comprises the number of tender joints (0=28), number of swollen joints (0-28), ESR (mm/hr) and visual analog scale for perceived pain (0-100). Disease activity assessed by DAS-28 was interpreted as low (DAS-28=2.6–3.2), moderate (DAS-28>3.2 to 5.1) or high (DAS28>5.1). Patients were considered in remission if DAS-28 was less than 2.6 [15]. RA patient's quality of life was evaluated using the Health Assessment Questionnaire (HAQ). The questionnaire investigates patients' ability to perform daily activities [16].

For the diagnosis of MetS, we adopted the Harmonized Joint Scientific Statement (HJSS) on metabolic syndrome recommendations. MetS criteria included increased blood pressure>130/85 mmHg, elevated FBS>100 mg/dL, obesity: waist circumference: >94 cm (male) >80 cm (female) or body mass index >30 kg/m<sup>2</sup>, dyslipidemia: triglycerides ≥ 150 mg/dL and high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL (male), 50 mg/dL (female). MetS was diagnosed in the presence of any three criteria [17].

Data obtained from the present study were statistically analyzed using SPSS 20 (IBM, USA). Numerical data were expressed as mean ± SD while categorical data were presented as number and percent.

#### Results

Comparison between the study groups regarding the clinical and laboratory data is shown in Table 1. Patients in GI had significantly higher DAS28 when compared with other groups. GII and GIII patients had significantly higher DAS28 when compared with GIV (Table 1 and Figure 1). It was also shown that GI patients had significantly higher PLR and NLR when compared with GIII. Similarly, GII patients had significantly higher PLR and NLR when compared with GIV (Table 1). Correlational analysis revealed a significant direct correlation between both PLR and NLR and DAS28 in the studied group. The correlation was weaker for NRL when compared with PLR (Table 2).

Logistic regression analysis identified presence of MetS [OR (95% CI): 19.9 (5.47-72.7), p< 0.001], increased PLR [OR (95% CI): 0.97 (0.95-0.98), p<0.001] and increased NLR [OR (95% CI): 0.06 (0.017-0.23), p<0.001] as significant predictors of high DAS28 in treatment-naïve RA patients. However, in multivariate analysis, only MetS [OR (95%CI): 8.66 (1.34-56.1), p=0.024] and increased PLR (OR (95%CI): 0.98 (0.96-0.99), p=0.002) remained significant (Table 3). In

**Table 1. Comparison between the studied groups regarding the clinical data.**

	G I Treatment-naïve + MetS N=50	G II Treatment-experienced + MetS N=50	G III Treatment-naïve N=50	G IV Treatment-experienced N=50	G V Controls N=50	P value
<b>Clinical findings</b>						
Age (years)	39.9 ± 9.2	44.3 ± 9.3	40.8 ± 8.5	43.4 ± 8.3	41.1 ± 11.4	0.1
Male/Female	7/43	11/39	10/40	08/42	08/42	0.83
Disease duration (months)	6 (4.8-7.0)*§	54.0 (48.0-84.0)#	5.0 (3.8-5.0)§	84.0 (60.0-120.0)	-	<0.001
Tender point count	6.0 (5.0-8.0)*§	2.0 (1.0-3.0)#	7.0 (6.0-8.0)§	2.0 (1.0-5.0)	-	<0.001
Swollen point count	7.0 (4.0-8.0)*§	2.0 (1.0-3.0)#	8.0 (7.0-9.0)§	2.0 (1.0-3.0)	-	<0.001
VAS	70.0 (65.0-80.0)*§	15.0 (10.0-30.0)#	65.0 (60.0-75.0)§	20.0 (10.0-30.0)	-	<0.001
DAS-28	5.9 (5.7-6.0)*#§	4.1 (3.2-5.5)§	4.9 (3.9-5.7)§	3.4 (2.7-4.0)	-	<0.001
HAQ	1.5 (1.2-1.8)*§	1.1 (1.0-1.2)#	1.7 (1.4-2.0)§	1.0 (1.0-1.1)	-	<0.001
<b>Laboratory data</b>						
ESR (mm/hr)	50.0 (46.0-52.0)*§¥	18.0 (12.0-28.0)#	48.0 (42.0-50.0)§¥	18.0 (12.0-28.0)	15.0 (12.0-19.0)	<0.001
CRP (mg/dl)	15.0 (12.0-18.0)*§¥	8.0 (4.0-10.0)#¥	16.0 (12.0-18.0)§¥	6.0 (4.0-8.0)¥	0.0 (0.0-0.0)	<0.001
Hemoglobin (gm/dl)	11.2 (10.9-11.5)§¥	11.9 (11.0-12.5)#¥	10.8 (10.4-11.1)§¥	12.1 (11.0-12.5)¥	13.50 (12.8-13.8)	<0.001
WBCs (× 10 <sup>3</sup> )	6.8 (5.7-7.8)	6.4 (5.5-7.6)	6.3 (5.4-7.8)	6.2 (5.5-7.6)	6.1 (5.5-7.2)	0.17
Platelets (× 10 <sup>3</sup> )	319.5 (296.5-351.8)#§¥	304.0 (284.8-330.3)#	276.0 (256.8-304.3)	293.5 (297.0-312.3)	298.0 (268.5-309.5)	<0.001
Neutrophils (× 10 <sup>3</sup> )	4.7 (4.0-5.3)§¥	4.4 (3.8-4.9)¥	4.1 (3.4-5.0)	3.9 (3.4-4.7)	3.7 (3.3-4.4)	<0.001
Lymphocytes (× 10 <sup>3</sup> )	1.40 (1.24-1.6)#§¥	1.61 (1.29-1.78)¥	1.72 (1.37-1.99)	1.67 (1.35-1.98)	1.8 (1.56-2.02)	<0.001
PLR	221.5 (193.1-269.3)#§¥	192.0 (169.2-232.2)#¥	161.6 (140.3-211.1)	173.8 (146.3-213.6)	162.8 (138.3-187.3)	<0.001
NLR	3.36 (3.03-3.68)*#§¥	2.78 (2.6-3.18)#§¥	2.44 (2.32-2.71)¥	2.31 (2.13-2.78)¥	2.14 (1.93-2.35)	<0.001
<b>Metabolic syndrome components</b>						
Obesity	50.0 (100.0)#§¥	50.0 (100.0)#§¥	19 (38.0)	22 (44.0 %)	20.0 (40.0)	<0.001
BMI (kg/m <sup>2</sup> )	33.2 (31.5-37.6)#§¥	32.5 (30.8-34.9)#§¥	26.9 (23.7-28.0)	27.1 (25.0-28.7)	26.1 (23.8-27.7)	<0.001
Waist circumference (cm)	94.0 (89.0-98.0)#§¥	92.5 (88.0-97.3)#§¥	77.5 (73.8-81.0)	79.0 (74.8-82.0)	78.0 (75.8-81.3)	<0.001
Increased blood pressure	20 (40.0 %)#§¥	21 (42.0)#§¥	-	-	-	<0.001
SBP (mmHg)	130.0 (120.0-140.0)#¥	130.0 (120.0-140.0)#¥	120.0 (110.0-120.0)§	120.0 (120.0-130.0)	120.0 (120.0-130.0)	<0.001
DBP (mmHg)	82.0 (80.0-90.0)#¥	80.0 (80.0-90.0)#¥	80.0 (70.0-80.0)	80.0 (80.0-90.0)	80.0 (80.0-80.0)	<0.001
Hyperglycemia	46 (92.0)#§¥	43 (86.0)#§¥	8 (16.0)	9 (18.0)	11 (22.0)	<0.001
FBG (mg/dl)	111.0 (105.0-118.0)#§¥	115.0 (109.5-123.8)#§¥	82.5 (79.8-96.0)	83.5 (80.0-88.0)	81.5 (78.8-88.0)	<0.001
Dyslipidemia	37 (74.0)#§¥	42 (84.0)#§¥	5 (10.0)	12 (24.0)	17 (34.0)	<0.001
Triglycerides (mg/dl)	178.0 (151.0-206.3)#§¥	153.0 (142.0-185.0)#§¥	120.0 (108.8-132.0)	103.0 (69.3-124.0)	118.5 (99.5-129.0)	<0.001
HDL (mg/dl)	50.0 (42.8-60.0)*	45.0 (39.5-49.0)#§¥	36.0 (35.0-40.0)	32.0 (30.0-35.8)	35.0 (31.0-39.0)	<0.001
<b>Treatment received</b>						
DMARDs	-	20 (40.0)	-	18 (36.0)	-	0.57
DMARDs + NSAIDs	-	27 (54.0)	-	26 (52.0)	-	
DMARDs + etanercept	-	3 (6.0)	-	6 (12.0)	-	
Data expressed as mean ± standard deviation (SD), median and interquartile range (IQR) or number and percent. *significant results versus G II, # significant results versus G III, § significant results versus G IV, ¥: significant results versus G V. BMI: Body Mass Index; CRP: C-Reactive Protein; DAS: Disease Activity Score; DBP: Diastolic Blood Pressure; DMARDs: Disease-Modifying Antirheumatic Drugs; ESR: Erythrocyte Sedimentation Rate; FBG: Fasting Blood Glucose; HAQ: Health Assessment Questionnaire; HDL: High-Density Lipoprotein; MetS: Metabolic Syndrome; NLR: Neutrophil Lymphocyte Ratio; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PLR: Platelets Lymphocyte Ratio; RA: Rheumatoid Arthritis; SBP: Systolic Blood Pressure; VAS: Visual Analog Scale; WBCs: White Blood Cells						

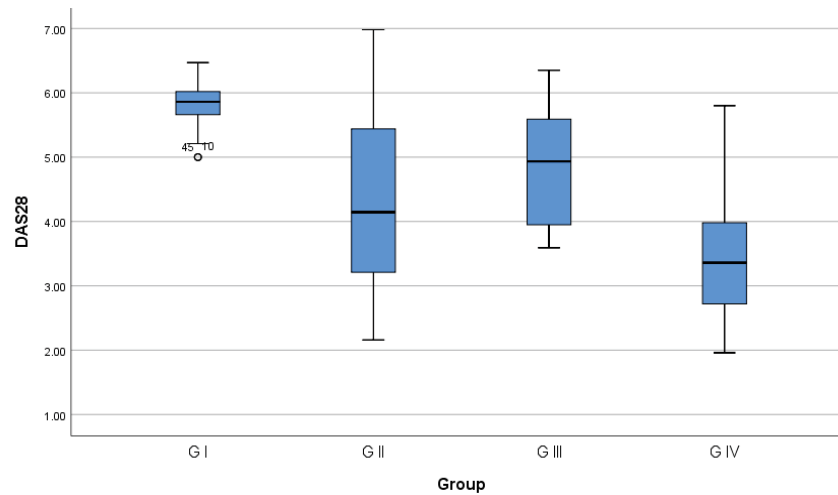


Figure 1. DAS 28 in the studied patients' groups.

**Table 2. Correlation between PLR, NLR and clinical and laboratory data in the studied patients groups.**

	G I				G II				G III				G IV			
	Treatment-naïve		Treatment-experienced		Treatment-naïve		Treatment-experienced		Treatment-naïve		Treatment-experienced		Treatment-naïve		Treatment-experienced	
	PLR	NLR	PLR	NLR	PLR	NLR	PLR	NLR	PLR	NLR	PLR	NLR	PLR	NLR	PLR	NLR
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
<b>Clinical findings</b>																
Age	-0.2	0.16	0.02	0.88	0.35	0.012	0.32	0.22	0.18	0.21	0.13	0.37	0.05	0.73	0.19	0.19
Disease duration	-0.32	0.025	-0.1	0.48	0.09	0.52	-0.004	0.98	-0.003	0.98	0.14	0.34	0.12	0.42	-0.02	0.88
Tender point count	0.06	0.69	-0.25	0.08	0.31	0.028	0.12	0.42	0.04	0.81	0.02	0.89	0.1	0.5	-0.04	0.78
Swollen point count	-0.13	0.39	-0.1	0.49	0.24	0.91	0.1	0.51	-0.06	0.67	0.21	0.14	-0.11	0.43	0.02	0.89
VAS	-0.01	0.94	0.07	0.63	0.35	0.012	0.19	0.19	-0.03	0.82	0.14	0.34	0.09	0.54	0.11	0.44
DAS-28	0.84	<0.001	0.32	0.024	0.65	<0.001	0.3	0.036	0.38	0.007	0.34	0.017	0.52	<0.001	0.29	0.042
HAQ	-0.22	0.13	-0.27	0.057	0.06	0.7	-0.03	0.83	0.01	0.92	0.06	0.69	-0.04	0.78	0.15	0.32
<b>Laboratory data</b>																
ESR	-0.13	0.37	0.07	0.61	0.32	0.25	0.22	0.13	-0.02	0.88	0.027	0.85	0.14	0.35	0.16	0.27
CRP	-0.005	0.97	-0.17	0.24	0.24	0.09	0.11	0.44	-0.04	0.76	0.06	0.7	0.07	0.61	-0.001	0.99
Hemoglobin	0.17	0.25	0.17	0.23	0.04	0.81	0.29	0.039	0.14	0.32	0.02	0.87	0.13	0.36	-0.03	0.83
WBCs	-0.68	<0.001	0.15	0.31	-0.75	<0.001	-0.17	0.25	-0.83	<0.001	-0.12	0.41	-0.84	<0.001	-0.18	0.22
Platelets	0.43	0.002	-0.02	0.89	0.22	0.13	-0.05	0.75	0.45	0.001	0.15	0.29	0.16	0.27	-0.22	0.12
Neutrophils	-0.63	<0.001	0.27	0.055	-0.72	<0.001	-0.08	0.59	-0.81	<0.001	-0.03	0.83	-0.76	<0.001	-0.04	0.79
Lymphocytes	-0.84	<0.001	-0.32	0.026	-0.89	<0.001	-0.62	<0.001	-0.91	<0.001	-0.44	0.001	-0.94	<0.001	-0.66	<0.001
<b>Metabolic syndrome components</b>																
BMI	-0.08	0.59	0.21	0.15	0.19	0.19	0.33	0.018	0.32	0.024	0.24	0.09	0.03	0.85	-0.14	0.32
Waist circumference	-0.01	0.92	-0.06	0.68	-0.05	0.73	0.15	0.31	0.06	0.7	-0.18	0.54	-0.08	0.58	-0.11	0.46
SBP	-0.29	0.045	0.06	0.66	0.19	0.18	0.14	0.32	0.16	0.28	-0.05	0.71	-0.06	0.69	-0.19	0.18
DBP	-0.24	0.097	-0.08	0.61	0.15	0.3	0.05	0.71	0.12	0.4	-0.06	0.68	-0.08	0.56	-0.26	0.07
FBG	-0.03	0.85	-0.07	0.61	-0.05	0.76	0.39	0.006	0.1	0.48	0.04	0.78	-0.02	0.88	-0.02	0.89
Triglycerides	0.17	0.24	0.1	0.5	-0.12	0.41	0.45	0.001	-0.14	0.35	-0.1	0.48	0.12	0.41	0.02	0.89
HDL	0.08	0.6	-0.09	0.54	-0.16	0.26	-0.4	0.001	0.03	0.85	0.14	0.33	-0.2	0.15	0.05	0.71

treatment-experienced patients, MetS [OR (95% CI: 2.71 (1.04-7.04), p=0.041] and increased PLR [OR (95% CI: 0.98 (0.97-0.99), p<0.001] were significant predictors of high DAS28 in univariate analysis. Only

increased PLR remained significant in multivariate analysis [OR (95% CI: 0.98 (0.96-0.99), p=0.001] (Table 4).

**Table 3. Predictors of high disease activity in treatment-naïve patients.**

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P	OR (95 % CI)	P
Age	1.0 (0.96-1.06)	0.80	-	-
Sex	1.27 (0.42-3.8)	0.68	-	-
Disease duration	1.04 (0.82-1.32)	0.72	-	-
MetS	19.9 (5.47-72.7)	<0.001	8.66 (1.34-56.1)	0.024
PLR	0.97 (0.95-0.98)	<0.001	0.98 (0.96-0.99)	0.002
NLR	0.06 (0.017-0.23)	<0.001	1.02 (0.17-6.0)	0.98

**Table 4. Predictors of high disease activity in treatment-experienced patients.**

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P	OR (95 % CI)	P
Age	0.99 (0.95-1.05)	0.89	-	-
Sex	1.99 (0.53-7.5)	0.31	-	-
Disease duration	1.01 (0.99-1.03)	0.079	1.0 (0.99-1.02)	0.36
MetS	2.71 (1.04-7.04)	0.041	2.8 (0.77-10.44)	0.12
PLR	0.98 (0.97-0.99)	< 0.001	0.98 (0.96-0.99)	0.001
NLR	0.43 (0.17-1.11)	0.08	3.08 (0.5-19.1)	0.23

**Discussion**

The present study aimed to assess and compare how the coexistence of MetS and RA can affect disease activity in treatment-naïve and treatment-experienced patients. Also, we sought to investigate if this coexistence is associated with the altered inflammatory conditions as expressed by the emerging hematological markers of inflammation PLR and NLR.

In our study, treatment-naïve and treatment-experienced RA patients with MetS had significantly higher disease activity when compared with their corresponding counterparts without MetS. Moreover, we identified MetS and an independent predictor of high disease activity in treatment-naïve and treatment-experienced RA patients. The association between disease activity in RA patients and MetS was previously reported [7,18-22]. However, other authors opposed this finding [23-25]. Of note, these studies recruited a substantial percentage of treated patients and didn't distinguish the effect of MetS on disease activity between treatment-naïve and treatment-experienced patients.

In our study, levels of the hematological markers of inflammation PLR and NLR showed diverse results in the studied groups. Both markers were significantly elevated in treatment-naïve patients with MetS in comparison to the corresponding group without MetS. Elevation of these markers in association with MetS was reported by other studies [26,27]. The increased inflammatory burden in RA patients with associated MetS is attributed to the additional inflammatory and immune mediators released by adipose tissues in those

patients [8]. Also, increased PLR and NLR were noted in RA patients [28].

However, in treatment-experienced patients, no significant differences were noted between RA patients with MetS and RA patients without. This may be explained by the anti-inflammatory effects of RA treatment that alleviate the added inflammatory burden of MetS in those patients. This explanation is supported by the weaker correlation between PLR and NLR and DAS28 in treatment-experienced patients. Our conclusions are supported by the study of Toms et al. [29] who noted that methotrexate use was associated with a lower risk of MetS in RA patients. Also, Dao et al. [19] identified less methotrexate use as a predictor of the presence of MetS in women with RA. Moreover, the studies of Bilecik et al. [30] and Abourazzak et al. [31] noted that the prevalence of MetS in patients with RA using methotrexate was significantly lower than without RA.

**Conclusion**

Metabolic syndrome is associated with elevated hematological markers of inflammation and disease activity in treatment-naïve RA patients. Both PLR and NLR are risk factors for RA activity in treatment-naïve patients with PLR being more strongly correlated with disease activity.

**Acknowledgments**

None

**Funding**

None

**Conflict of interest**

Authors declare that there is no conflict of interest.

**Author contributions**

Conception and design: AG; Data analysis, acquisition, and interpretation: HA, AA; Manuscript writing: AG; Critical revision: HA, AA; Agreement: All authors; Accountability: AG

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