

## Correlation of Platelet to Lymphocyte Ratio with Presence and Severity of Metabolic Syndrome

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### Abstract

**Objective:** The aim of this study is to evaluate the relation between the components of Metabolic syndrome (MS) and the inflammation and the platelet-to-lymphocyte ratio (PLR) recognized as a novel marker of pro-thrombotic state.

**Method:** 70 patients with MS criteria were included in the study. 70 healthy people with matching age and gender characteristics were included in the study as the control group. The patients were divided into three groups with regard to the number of MS characteristics: Group 1 (the patients with three MS criteria), group 2 (the patients with four MS criteria), and group 3 (the patients with five MS criteria). PLR was calculated in regard to the complete blood count.

**Results:** The patients with MS had significantly higher PLR level compared to those without MS. However, PLR level were not associated with severity of MS. A moderate positive correlation was revealed between the severity of MS and PLR ( $r=0.419$ ,  $p<0.001$ ) and a strong positive correlation between the severity of MS and hs-CRP ( $r=0.562$ ,  $p<0.001$ ). Also, a positive correlation was detected between hs-CRP and PLR in our patient population ( $r=0.281$ ,  $p=0.002$ ). In order to specify the level of PLR to predict MS, ROC curve analysis was performed. The cut-off level for PLR with optimal sensitivity and specificity was calculated as 0,132 (Area under curve [AUC] =0.744 [0.655-0.833],  $p<0.001$ ). For that level, the sensitivity was 73% and the specificity was 68, 4%.

**Conclusion:** This is the first study which determines the fact that there is a relation between MS criteria, the inflammation and PLR, which is a new marker of the pro-thrombotic state. There is also a positive correlation between PLR and hs-CRP in these patients. PLR may be beneficial in predicting the adverse cardiovascular cases in the patients with MS.

**Key words:** Metabolic Syndrome, Platelet/lymphocyte ratio, Inflammation

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### Introduction

Metabolic syndrome (MS) is a case basically beginning with insulin resistance (IR), containing a combination of the systemic disorders such as abdominal obesity, glucose intolerance or diabetes mellitus, dyslipidemia, hypertension and coronary artery disease (CAD), and accompanied by vascular inflammation and pro-thrombotic tendency. The prevalence of metabolic syndrome increases with the increased physical inactivity and the central obesity in our society (Bloomgarden, 2003). MS includes more than one risk factor in terms of cardiovascular diseases. IR, which is one

of the basic pathological mechanisms composing MS, is related to especially proinflammatory and pro-thrombotic state (Calles-Escandon et al., 1998 and Hori et al., 2005). Pro-thrombotic and proinflammatory tendency has an important role in the exacerbation of the atherosclerotic process and the formation of serious clinical states.

The studies carried out demonstrate the relation between the components of MS and the tendency to proinflammatory state. A simple indicator of proinflammatory state in the patients with MS is the detection of the increased C - reactive protein (CRP) in these patients. It is additionally known that the levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- $\alpha$ ) increase in these patients (Yudkin et al., 1999). Inflammation is known to have a role in the onset and the progress of atherosclerotic illnesses (Hansson et al., 2005). Platelet-to-lymphocyte ratio (PLR) has recently been identified as a biological indicator of the balance between inflammation and thrombosis especially in the patients with malignancy (Smith et al., 2008; Wang et al., 2013). There are evidences about the negative consequences of the increase in PLR in the cardiovascular diseases (Azab et al., 2012; Acar et al., 2013). The aim of this study is to assess the relationship between MS, its components and PLR, which has recently been recognized as an inflammation and pro-thrombotic indicator.

### Materials and Methods

In a retrospective longitudinal study, our study population consisted of non-selected 194 patients, who visited our clinic from January to August. The exclusion criteria were determined as infection (n:4), chronic systemic inflammatory diseases (n:5) and the patients using drug affecting the number of leukocytes (steroid, chemotherapeutic etc.) (n:3). Also, the patients with renal failure (n:6), liver failure (n:3), secondary hypertension (n:16) and known coronary artery disease (n:9), heart failure (n:7), and severe heart valve diseases (n:4) were excluded from the study. Finally, the study population consisted of 140 patients (n:70 patients who had metabolic syndrome, n:70 age- and sex-matched healthy subjects). All participants gave an informed consent and the study was approved by the local ethics committee.

For the diagnosis of MS, National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP ATP 3) were used (Adult Treatment

Panel III, 2001) The presence of 3 or more criteria below was accepted as MS.

1- Hypertension: Existing antihypertensive therapy or blood pressure  $\geq 130/85$  mm/Hg

2- Dyslipidemia: Plasma triglyceride (TG) level  $\geq 150$  mg/dL ( $\geq 1.7$  mmol/L)

3- Low HDL cholesterol level: In women  $< 50$  mg/dL ( $< 1.3$  mmol/L), in men  $< 40$  mg/dl ( $< 1.0$  mmol/L)

4- Abdominal Obesity: Waist circumference (WC) in men  $> 102$  cm, WC in women  $> 88$  cm

5- Glucose: Fasting blood glucose  $\geq 110$  mg/dL ( $\geq 5.6$  mmol/L) Type 2 DM or impaired glucose tolerance test.

The patients were divided into three groups with regard to the number of MS characteristics: Group 1 (the patients with three MS criteria), group 2 (the patients with four MS criteria), and group 3 (the patients with five MS criteria).

Blood Pressure (BP) was measured after at least 15-minute rest in sitting position. The mean of all three measurements with five-minute intervals were considered as BP. High sensitive C-Reactive protein (hs-CRP), total cholesterol, TG, HDL, LDL levels, urea, creatinine and plasma glucose were measured in the venous blood samples obtained in the morning after eight-hour fasting. The complete blood count was studied in our hematology unit with Beckman-Coulter Gen-S system device (Beckman-Coulter Inc., USA). The weight, height, and WC were measured while fasting and standing up by the standard measuring tools. The narrowest diameter between costal arch and anterior superior iliac spine was measured for WC. Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) and body surface area (BSA) ( $\text{m}^2$ ) were calculated using the formulas "weight ( $\text{kg}$ )/height ( $\text{m}$ )<sup>2</sup>" and "BSA ( $\text{m}^2$ )= 0.007184 x Height ( $\text{cm}$ )<sup>0.725</sup> x Weight ( $\text{kg}$ )<sup>0.425</sup>" respectively.

#### Statistical analysis:

Independent sample *t* test or Mann-Whitney *U* test were used for continuous variables, and chi-square test for categorical variables. One-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used to compare more than two groups. Correlations were assessed using Spearman's test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off level of PLR to predict the metabolic syndrome. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Version 15.0 (SPSS Inc., Chicago, Illinois). Continuous variables

were defined as mean  $\pm$  standard deviation, and categorical variables were given as percentages. Any *P* value  $<0.05$  was considered as statistically significant.

### Results

70 patients with MS and 70 people with matching age and gender as the control group were included in the study. The characteristics of two groups were summarized in Table 1. As showed in Table 2, while the number of neutrophils, white blood cells (WBC) and lymphocyte were higher in the patients with MS than the control group, the platelet count and the hemoglobin level were found similar.

**Table-1:** Differences between clinical and laboratory parameters of the groups with and without metabolic syndrome

	MS (-)	MS (+)	P value
Age (years)	47,0 $\pm$ 13,7	48,3 $\pm$ 9,51	0,542
WC	85,75 $\pm$ 10,9	97,8 $\pm$ 10	$<0,001$
BMI (kg/m <sup>2</sup> )	24,5 $\pm$ 3,92	29,2 $\pm$ 5,51	$<0,001$
FBG (mmol/L)	5,0 $\pm$ 0,77	6,2 $\pm$ 1,48	$<0,001$
TG (mmol/L)	1,46 $\pm$ 0,56	2,38 $\pm$ 1,12	$<0,001$
HDL (mmol/L)	1,23 $\pm$ 0,20	0,95 $\pm$ 0,22	$<0,001$
LDL (mmol/L)	2,7 $\pm$ 0,84	3,00 $\pm$ 0,59	0,028
SBP (mmHg)	129 $\pm$ 15,7	134 $\pm$ 18,8	0,086
DBP (mmHg)	81,1 $\pm$ 10,45	85,3 $\pm$ 9,72	0,024

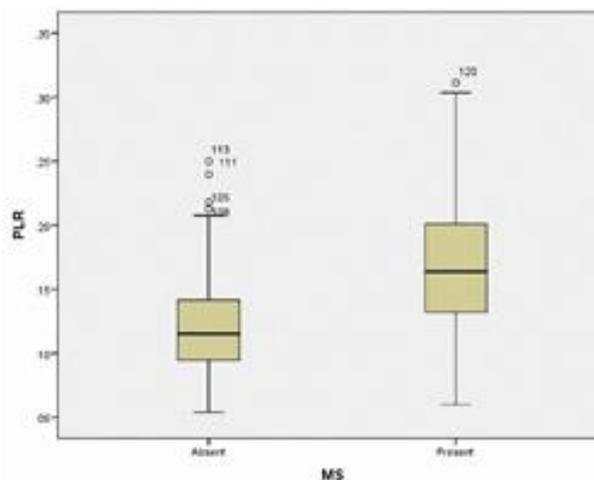
MS: Metabolic syndrome, WC: Waist Circumference, BMI: Body Mass Index, FBG: Fasting Blood Glucose, TG: Triglycerides, DL: High Density lipoprotein, LDL: Low Density lipoprotein, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

**Table-2:** The hematologic parameters of the groups with and without metabolic syndrome

	MS (-)	MS (+)	P value
WBC	6560 $\pm$ 983	7150 $\pm$ 1442	0,010
Hemoglobin (g/dL)	13,5 $\pm$ 0,5	13,5 $\pm$ 0,50	0,562
PLR	0,12 $\pm$ 0,04	0,016 $\pm$ 0,05	$<0,001$
Platelet count ( $\times 1000$ )	282,6 $\pm$ 66,3	288,1 $\pm$ 67,7	0,653
Lymphocyte Count	2431 $\pm$ 551	1823 $\pm$ 501	$<0,001$
Neutrophil Count	3984 $\pm$ 817	5182 $\pm$ 1171	$<0,001$
Hs-CRP	0,65 $\pm$ 0,33	1,12 $\pm$ 0,49	$<0,001$

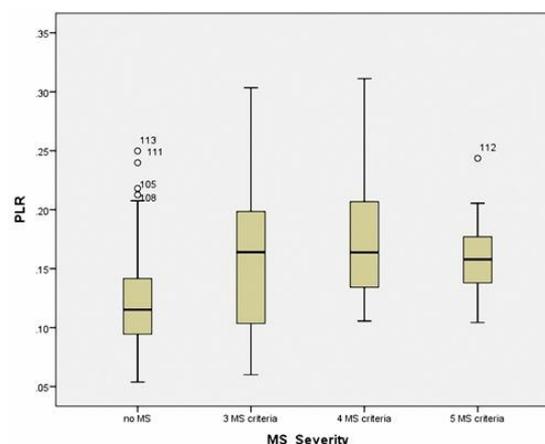
MS: Metabolic Syndrome, WBC: White Blood Cells, PLR: Platelet to Lymphocyte Ratio, Hs-CRP: High sensitive-C reactive protein

Also, hs-CRP level was significantly higher in MS group than the control group (1.15 $\pm$ 0.52 vs 0.64 $\pm$ 0.34,  $p<0.001$ ). (Figure-1).



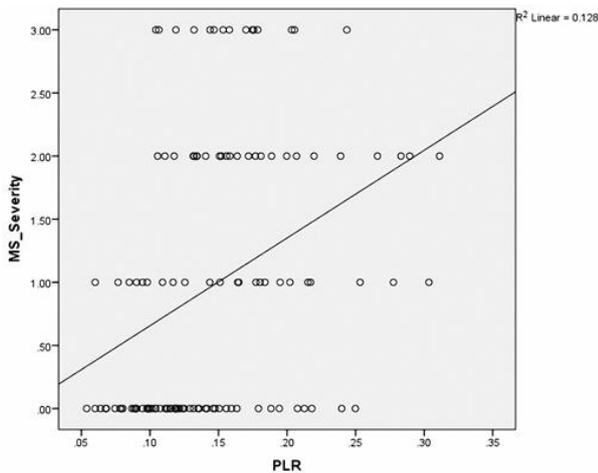
**Figure-1:** PLR values according to MS

The patients with MS had significantly higher PLR level compared to those without MS. However, PLR level were not associated with severity of MS (Figure 2).

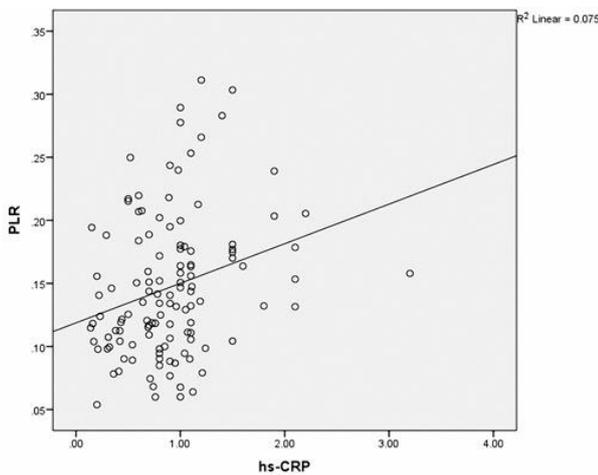


**Figure-2:** PLR values according to MS severity

A moderate positive correlation was revealed between the severity of MS and PLR ( $r=0.419$ ,  $p<0.001$ ) and a strong positive correlation between the severity of MS and hs-CRP ( $r=0.562$ ,  $p<0.001$ ) was found (Figure 3 and 4).



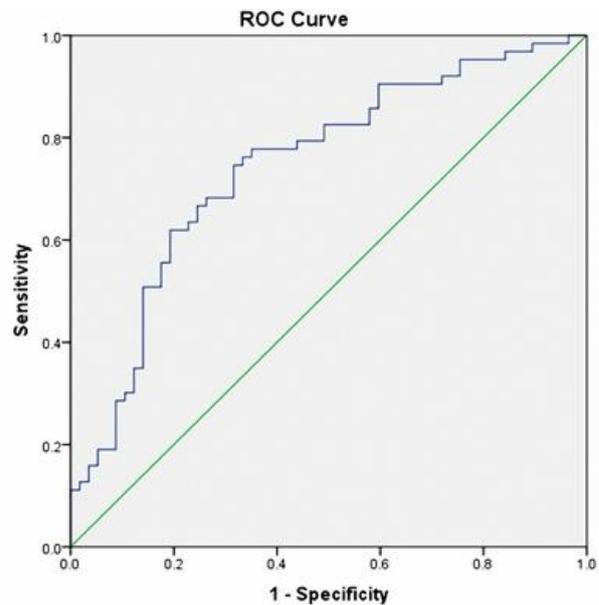
**Figure-3:** Correlations of MS severity with PRL



**Figure-4:** Correlations of PRL with hs-CRP

Also, a positive correlation between hs-CRP and PLR was detected in our patient population ( $r=0.281$ ,  $p=0.002$ ). In the subjects without MS, PLR was detected to be significantly lower compared to those with MS meeting three, four, and five criteria ( $0,12\pm0,04$  vs  $0,16\pm0,06$ ,  $0,18\pm0,06$ , and  $0,16\pm0,04$ ). However, there were no differences between the patients meeting three, four and five MS criteria ( $0,16\pm0,06$ ,  $0,18\pm0,06$ , and  $0,16\pm0,04$ , three vs four  $p:0,169$ , three vs five  $p:0,963$ , four vs five  $p:0,241$ ).

In order to specify the level of PLR to predict MS, ROC curve analysis was performed. The cut-off level for PLR with optimal sensitivity and specificity was calculated as 0,132 (Area under curve [AUC] =0.744 [0.655-0.833],  $p<0.001$ ). For that level, the sensitivity was 73% and the specificity was 68,4% (Figure 5).



**Figure-5:** Receiver–operating characteristic (ROC) curve analysis plot to determine the cutoff value of PRL in MS

### Discussion

As a summary of the results of this study; firstly, an important correlation between the inflammation and PLR, which was recognized as an indicator of pro-thrombotic progress, was detected. Secondly, there was no correlation between the increase in PLR and the increase in the number of MS criteria. Thirdly, a significant relation between PLR and hs-CRP level associated with inflammation in the patients with MS was detected. The data obtained in this study about the relation between PLR and MS is the first findings in the Literature.

MS arises from the combination of the metabolic sourced risk factors increasing the development of atherosclerosis, and is a metabolic disorder based on IR (Moreno et al., 2004). The classical components of MS are the increased BP, atherogenic dyslipidemia, glucose intolerance, central obesity, vascular inflammation and pro-thrombotic state. These components demonstrate the treatment goals in addition to the diagnosis of metabolic (Bloomgarden, 2003). The relation of almost all of MS components with the systemic inflammation was presented (Fröhlich et al., 2000). The simplest indicator of the increased proinflammatory state in the patients with MS is the increased C-reactive protein level. Moreover, as the number of MS components increases, the amount of C-reactive protein increases, too. The increased C-reactive protein amount is related to the increased cardiovascular cases (Ridker et al.,

2003). This causes to think that both diabetes mellitus and atherosclerosis may be related to the inflammation (Haffner et al., 2006).

In the case of obesity, proinflammatory and proatherogenic cytokines, one of the criteria composing MS, such as IL-6, TNF- $\alpha$ , resistin, visfatin, the omentum, leptin, plasminogen activator inhibitor -1(PAI-1) and many bioactive adipokine are released from the increased adipose fat tissue (Mazurek et al., 2003; Baker et al., 2006; Fain et al., 2008). IL-6 level, one of these inflammatory cytokines increases in parallel with the fat tissue, and IL-6 also induces the production of C-reactive protein. The numerous inflammatory cytokines released from the adipose tissue such as TNF- $\alpha$  and IL-6 induce the inflammatory activity, an important part of the atherosclerotic process (Chan et al., 2005). PLR is an important inflammatory marker found in the recently performed studies; and it was detected to be related to the major negative cardiovascular cases (Azab et al., 2012).

The hyperglycemic state consisted as a result of IR leads to the abnormalities in the coagulation system, and causes to the pro-thrombotic environment at the result of the platelet dysfunction and the generation of thrombin (Desouza et al., 1999). One of the best indicators of the pro-thrombotic state in the patients with MS is the increased PAI-1 and the fibrinogen level in the patients with obesity. The fibrinogen reflects the inflammatory activity as an acute phase reactant, and as well as is recognized as one of the new risk factors (Ross et al., 1999). This increases the tendency to the generation of thrombus leading to the development of acute coronary cases. It is a fact known for a long-term that the platelet activation and the aggregation have a role in the pathophysiology of acute coronary syndromes (Vaughan et al., 2002). For example; there is a correlation between the mean platelet volume (MPV) and the functional status of platelets. In many studies, it was showed that MPV was higher in the patients with CAD and acute coronary syndrome in proportion to the normal individuals (Kishk et al., 1985; Bath et al., 1996). Moreover, MPV was detected to be an independent indicator of reperfusion and mortality (Huczek et al., 2005). Therefore, the platelet activation has an important role in the onset and the progress of atherosclerosis (Tsiara et al., 2003). On the other side, there are studies suggesting that the low number of lymphocytes composing PLR in peripheral blood

lymphocytes composing PLR in peripheral blood is related to the major cardiac negative cases (Ommen et al., 1997; Acanfora et al., 2001). Thus, PLR is recognized as a new marker compounding both two hematological parameters, and has been detected to be related to some major negative cardiovascular cases in a certain number of recent studies. It was also detected that the high level of PLR was an indicator of long-term mortality in non-ST elevation myocardial infarction (Azab et al., 2012).

This is the first study about this subject performed in the patients with MS although there are previous studies determining the relationship between PLR and the negative cardiovascular cases. The high PLR in the patients with MS may be the beginning and the predictor of the increased procoagulant and proinflammatory state, and may be the preview of the adverse cardiovascular events in these patients.

#### **Limitations**

The most important limitation of the study is the low number of the patients included in the study. The second one is to make the assessment supposing that each component of MS has the same effect. It could be more beneficial to evaluate the individual differences of the components of MS and to analyze their relations with PLR one by one. But, this could not be performed as the patient number was insufficient for the subgroup analysis.

#### **Conclusion**

This study is the confirmation of the existence of the increased inflammation in the patients with MS by PLR which is a new marker. This study is important from the clinical view as it suggests that PLR may be used in predicting the adverse cardiovascular cases in the patients with MS and the beginning of the cardiovascular disease development.

**Informed Consent:** Verbal informed consent was obtained from patients who participated in this study

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept YK.; Design AK.; Supervision AK.; Materials YK,AK; Data Collection and/or Processing YK, OB, ZYG, AB.; Analysis and/or Interpretation ZYG; Literature Review MKÇ OB; Writing OB; Critical Review YK

**Conflict of Interest:** No conflict of interest was declared by the authors.

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