A Study of Platelet to Lymphocyte Ratio in Patients with Metabolic Syndrome

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Abstract: _Background: The incidence and prevalence of the metabolic syndrome varies all over the world, showcasing the age and ethnicity of the populations taken into account and the diagnostic criteria applied. Various studies have indicated an association of Metabolic Syndrome (MS) and insulin resistance (IR) with inflammation. Platelet-lymphocyte ratio (PLR) has emerged as a novel inflammatory index that may reflect the extent of inflammation and overall mortality. This study aims to evaluate the PLR in patients with MS and to establish its correlation with the severity of MS._ _Methods: A cross sectional study was conducted on 250 outpatient subjects at SRMS Hospital, Bareilly (125 subjects with Metabolic Syndrome and another 125 age and gender matched control participants without Metabolic Syndrome). Thorough history including history of risk factors if any, physical examinations and basic investigations like complete blood counts, Fasting and Random blood sugars HbA1c levels, fasting lipid profile, ECG were done and the data was analyzed and interpreted using appropriate statistical methods._ _Results: PLR when compared was 6.9% higher in male's subjects as compared to female's subjects with metabolic syndrome. PLR was 95.9% higher in subjects with metabolic syndrome as compared to subjects without metabolic syndrome (p<0.05). Also, there was a rise in PLR in male subjects as severity of metabolic syndrome increased._ _Conclusions: In this study, PLR beyond 90 ruled in favour of significant inflammation. PLR is calculated from complete blood count along with differential leucocyte count. It is an affordable, easily and widely available marker of inflammation, which can help in the risk stratification of patients with various cardiovascular diseases along with the traditionally used markers._

Keywords: Insulin resistance, Metabolic syndrome

1. Introduction

In India, prevalence of metabolic syndrome ranges from 11% to 41% .1 Numerous studies have demonstrated an association between metabolic syndrome-insulin resistance and inflammation. The relationship of MS with inflammation has been explained by two hypotheses. The first hypothesis states that chronic low-grade inflammation leads to metabolic disturbances, which then leads to insulin resistance. 2 The second one hypothesises that altered glucose and lipid metabolism trigger inflammation which in turn leads to insulin resistance.3

Several studies have also exhibited the relationship of systemic inflammatory markers high-sensitivity CRP (hs-CRP) with metabolic syndrome and insulin resistance.4 Higher levels of inflammatory markers (hs-CRP) was seen in prediabetic patients with insulin resistance. Hence, a proinflammatory state can add to the atherogenic risk profile in prediabetic patients with increased insulin resistance.5 However, most of these markers are tedious and costly.

Platelets and leukocytes are the important units of these processes that leads to the development of atherosclerosis. Platelet-to-lymphocyte ratio (PLR) is a new prognostic marker that incorporates the risk prediction of these 2 parameters and gives an overview of both the aggregation and inflammation pathways.6 Authors hypothesized that with Platelet-to-lymphocyte level, one could assess the severity of inflammation in metabolic syndrome.

2. Methods

A cross sectional study was conducted on 250 patients seen on outpatient basis at SRMS Hospital, Bareilly. Out of the 250 patients, 125 were with Metabolic Syndrome and another 125 age and gender matched control participants were without Metabolic Syndrome. The study was done between July 2019 to March 2020.

Inclusion criteria
Patients of age ≥18yrs, fulfilling the National Cholesterol Education Program and Adult Treatment Panel III (NCEP: ATP III) modified criteria of Metabolic Syndrome and with normal systemic examination.

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria 3 (NCEP ATP 3).7 Presence of 3 or more of the following are required according to those criteria:

- Abdominal obesity (waist circumference [WC] >102 cm in men and >88 cm in women);
- A high blood pressure (BP; systolic, >130 mm Hg; and/or diastolic, >85 mm Hg);
- A high fasting blood glucose (FBG) concentration >5.6 mmol/L (>110 mg/dL);
- A high triglyceride (TG) level >1.7 mmol/L (>150 mg/dL);
- A low high-density lipoprotein (HDL) cholesterol level<1.3 mmol/L for women, and <1.0 mmol/L for men (<50 mg/dL for women and <40 mg/dL for men).

Exclusion criteria
Patients on medications (except for oral hypoglycemic and lipid lowering drugs) that could have possibly affected the results of the study and inflammation parameters, patients with history of alcohol consumption/smoking, patients taking immunosuppressive drugs, and patients diagnosed with coronary artery disease.

Detailed history was taken. Thorough physical examinations and baseline investigations like complete blood counts, fasting and random blood sugars, HbA1c levels, fasting lipid profile, ECG were done. Subjects were divided into 3 groups on the basis of the number of metabolic syndrome criteria: Group 1 (subjects satisfying 3 metabolic syndrome criteria), group 2 (subjects satisfying 4 metabolic syndrome criteria),

and group 3 (subjects satisfying 5 metabolic syndrome criteria).

Height, weight, and waist circumference were measured while fasting and standing up with standard measuring apparatus. For waist circumference, the narrowest diameter between costal arch and anterior superior iliac spine was measured. The blood pressure was measured in sitting position after at least a 10-minute rest in that position. The mean of all 3 measurements with a 2-minute interval was considered as blood pressure.8 Data was analyzed using simple statistical methods and were shown categorically in tables and figures.

3. Results

Out of the 250 subjects, 115 were females and 135 were males (Figure 1).

Figure 1: Gender wise classification of the subjects.

Out of the 115 females, 54 had MS and 61 subjects did not qualify for MS. Similarly out of the 135 male subjects, 70 were metabolic syndrome and 65 were non metabolic syndrome. Mean age group of the study population was 45-65 years.

The PLR ratio in patients with MS was higher than those without MS. Also, platelet to lymphocyte ratio increased as severity of MS increased (Figure 2). In subjects without metabolic syndrome, platelet to lymphocyte ratio was found to be much lower as compared to those with metabolic syndrome meeting 3, 4, and 5 criteria. Platelet-lymphocyte ratio increased in males with metabolic syndrome as age progressed whereas it declined in females with age (Table 2). Metabolic syndrome comprises of multiple and interrelated risk factors of metabolic origin that seem to directly increase the chance of development of atherosclerosis. The metabolic risk factors comprise of atherogenic dyslipidemia (high TGs, lowered HDL cholesterol concentrations), elevated BP, plasma random and fasting glucose, prothrombotic state, and inflammatory state.6

Though both hereditary and environmental factors contribute to the development of metabolic syndrome, only little is known about the underlying pathogenesis. All the components that make up metabolic syndrome were seen to be associated with systemic inflammation.9

Furthermore, inflammation has recently been recognised as an independent risk factor for atherosclerosis and cardiovascular disease. Leukocyte activation seems to occur during an inflammatory reaction which in turn leads to atherogenesis and thrombus formation. As inflammation and leukocyte subtypes affect every stage of atherosclerosis, it is easy and important to study parameters that exhibit the progression of atheromatous plaque.9

In atherosclerosis, inflammation inhibits the anti-adhesion properties of platelets, which in turn leads to increase in the interaction of platelets with the endothelium. This leads to activation of inflammatory effects in cascade, similar to the one that occur in thrombosis and haemostasis. Increased platelet activation triggers the secretion of cytokines which in turn leads to "chemotaxis" effect, also known as "inflamed endothelium". Interaction between platelets and leukocytes promotes cell recruitment in the area of the lesion through selections and integrins.10

The study concluded that there was significantly higher platelet to lymphocyte ratio in subjects with metabolic syndrome as compared to subjects without metabolic syndrome and also, as severity of metabolic syndrome increases platelet to lymphocyte ratio also increases. Younger females have higher levels of inflammation (higher platelet to lymphocyte ratio) which decreases as age progresses and in males, the platelet to lymphocyte ratio increases as age progresses.

The platelet to lymphocyte ratio is less investigated as compared to neutrophil to lymphocyte ratio. Sex difference in platelet to lymphocyte ratio is seen, being higher in women than in men. The difference is attributed to higher platelet counts in women. The mechanisms undrelying sex-related difference in platelet count is not well known. One hypothesis is that there is lower serum iron in menstruating and elder women, which triggers platelet production. Additionally, difference in estrogen level in males and females may be also play a role. It was seen that estrogens favour platelets formation in mouse. Platelet count also varies with age, being higher in young than in old age, which may be related to hematopoietic stem cell reserve. In elderly, a reduction in hematopoietic stem cell reserve leads to a reduction of the platelets formation.11

In a study done by Lishan Wu et al who calculated platelet to lymphocyte ratio on Chinese Han population from Chaoshan region in South China found somewhat similar results with neutrophil to lymphocyte ratio. Young females aged 30-49 years had a higher NLR than the males while the NLR in males between ages 60~69 was higher than in females. Females have a higher than males.11

4. Conclusion

According to this study, Platelet-lymphocyte ratio above 90 indicates significant inflammation. Platelet to lymphocyte ratio is calculated from complete blood counts with differential count, and is inexpensive, easily and widely available marker of inflammation and can aid in the risk stratification of patients with cardiovascular co morbidities. More prospective studies are needed to confirm the findings of this study and the optimal cut-off value of PLR in inflammation.

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Table 1: Comparison of Mean PLR between the groups

Criteria	Female	Male
5/5	186.32±24	182.55±22.7
4/5	140.10±16.6	130.35±19.61
3/5	110.89±17.80	110.60±13.4
NON MS	80.95±11.5	76.95±14.1

Table 2: Comparison of Mean PLR between males and females

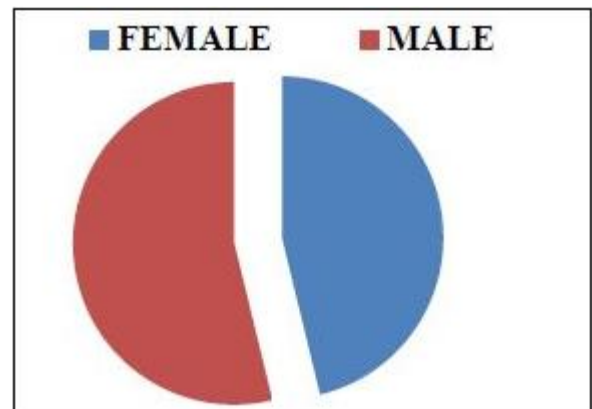| Age (years)	Female	Male
<45	128.46±21.5	89±20.4
45-65	110.44±24.5	107.03±18.5
>65	90.45±21.8	112.72±26.8

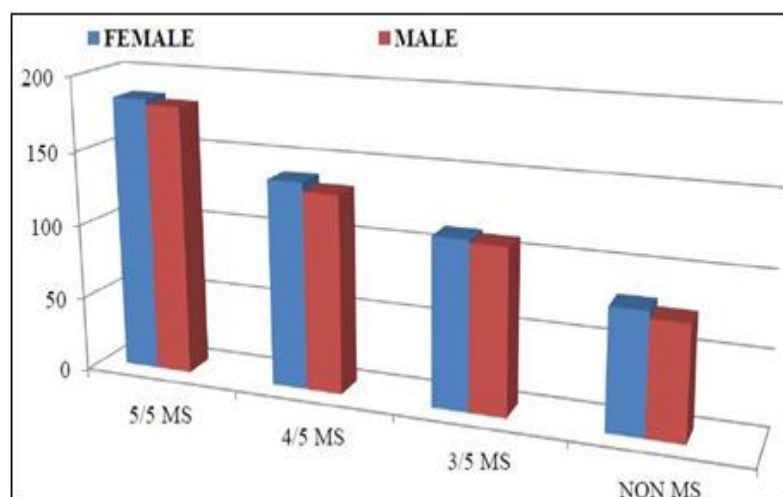

Figure 1: Gender wise classification of the subjects

Figure 2: Comparison of the mean PLR between the groups