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Research Article

TO STUDY BLOOD COUNT PARAMETERS CAN PREDICT THE SEVERITY OF CORONARY ARTERY DISEASE

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of death worldwide. CAD is an inflammatory, progres sive disease and atherosclerosis has a pivotal role in the etiology. The aim of this study was to investigate the relationships between some prominently hematologic blood count parameters (mean platelet volume [MPV], neutrophil to lymphocyte ratio [NLR]) and the severity of CAD by using Gensini scores. A total of 194 patients, who had undergone coronary ngiography, enrolled in this study. The control group consisted of 42 patients who had normal coronary arteries. Remaining CAD patients were divided into two groups accord ing to their Gensini scores. NLR and MPV were higher in the severe atherosclerosis group compared with the mild atherosclerosis group ($p = 0.007$, $p = 0.005$, respectively). The Gensini score showed significant correlations with NLR ($r = 0.20$, $p = 0.011$), MPV ($r = 0.23$,$p = 0.004$) and high density lipoprotein cholesterol ($r = –0.161$, $p = 0.047$). Using a cut-off level of 2.54, NLR predicted severe atherosclerosis with a sensitivity of 74% and specificity of 53% (area under curve [AUC], 0.627; 95% confidence interval [CI],0.545 to 0.704; $p = 0.004$). Our study suggests that both NLR and MPV are predictors of severe atherosclerosis and may be used for the prediction and identification of cardiac risks in CAD patients.

Keywords :- Neutrophil to lymphocyte ratio; Mean platelet volume; Gensini score; Coronary artery disease.

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INTRODUCTION

The health status of human societies has been historically associated with their social and economic development. With industrialization,cardiovascular disease (CVD) prevalence seriously compromises the health of populations worldwide. Screening and identifying risk factors are essential to prevent and control CVD. Generally, routine blood tests help in the early diagnosis of diseases, thereby facilitating the physicians with information regarding inflammatory processes.[1] Hematological parameters obtained using blood investigations mainly include classifying and quantifying white blood cells (WBCs), red blood cells (RBCs), and platelets.

Atherosclerosis is a chronic inflammatory process caused by the accumulation of lipids, fibrous elements and calcification in the arteries. This chronic arterial disease starts with endothelial activation,followed by a cascade of events involving vasoconstriction and activation of the inflammatory process leading to the formation of atherosclerotic plaque [2]. Atherosclerosis, as an inflammatory disease, is crucial for the onset and development of coronary artery disease (CAD) because inflammation plays an important role in the formation and progression of atherosclerosis. [3]. CAD remains the leading cause of mortality and morbidity worldwide. Therefore, the identification of high-risk patients with CAD is useful for clinical management and prognosis [4].

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Some calculated total blood count readings are investigated as additional readings to help with evaluation of CAD patients' condition, clinical management, and prognosis. Markers of inflammatory processes, such as neutrophil-to-lymphocyte ratio (NLR) [5], monocyte-to lymphocyte ratio (MLR) [6], and platelet-to-lymphocyte ratio (PLR) [7], have been shown to be associated with the severity of CAD and poor cardiovascular prognosis.

Higher band neutrophil counts were related to increased atherosclerosis severity in coronary arteries [8]. Moreover, several studies have recently suggested the neutrophil to lymphocyte ratio (NLR) as a new inflammatory biomarker for vascular risks and cardiac mortality [9-11]. The relationship between CAD and NLR has been investigated by many studies, but only limited data exists for the association of NLR with extensive and severe level of CAD. Furthermore, since it has been discovered that platelets have an important role in the initiation and extension of CAD, appreciable interest has been directed toward platelets [12]. Large platelets are more active in terms of enzymatic and metabolic efficacy and have high thrombotic potential. Mean platelet volume (MPV) is an indicator of large platelets and platelet activation [13]. MPV has been shown to be increased in some cardiovascular events, like unstable angina and myocardial infarction [14-15]. But studies about the relationship between MPV and the severity of CAD have suggested conflicting evidence.

The prognostic situation of the CAD patients is closely related to the severity of atherosclerosis [16]. In this regard, the prediction and identification of severe atherosclerosis takes up a large share in the clinical practice of CAD patients. In accordance with this idea, we investigated the relationships between NLR, MPV and the severity of CAD by using Gensini scores (GS)

MATERIAL AND METHODS

We consecutively enrolled a total of 194 patients who were admitted to Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry and Sree *Balaji Medical College* & Hospital,Chennai for coronary angiography procedures between January 2016 and January 2017. All patients had anginal symptoms and/or positive myocardial perfusion scintigraphy or stress test results, or some electrocardiographic changes pointing to ischemia. Acute coronary syndrome history (less than 1 month), recent coronary intervention, heart failure, valvular heart diseases, the existence of inflammatory diseases, severe renal and hepatic diseases, active malignancy, malnutrition and pregnancy were all exclusion criteria. Patients with arterial blood pressure measurements above 140/90 mmHg or a history of current antihypertensive drug use were considered hypertensive. The presence of diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) above 126 mg/dL or a history of actual antidiabetic drug use. The study was approved by the Local Ethics Committee and informed consent was received from all patients before coronary intervention.

Baseline variables:

Before the procedure, baseline demographic and clinical data like age, gender, weight, the presence of chronic diseases (DM, hypertension, etc.), complete blood count parameters, FPG, lipid parameters, and serum creatinine were all obtained from the medical records of the patients. Hemoglobin, WBC, platelet, MPV, lymphocyte, and neutrophil counts were all measured with an auto-analyzer (Sysmex XE-2100, Sysmex, Kobe, Japan). NLR was calculated by dividing the neutrophil count with the lymphocyte count. The estimated glomerular filtration rate (eGFR) was calculated by using the simplified Modification of Diet in Renal Disease equation [17].

Coronary angiography and severity of coronary atherosclerosis:

The Judkins technique was used for the coronary angiography. All angiography results were evaluated by two experienced cardiologists who did not have clinical knowledge about the patients. The presence of at least 50% luminal atheromatous stenosis in at least one coronary artery was considered as CAD [18]. Patients with normal coronary arteries were considered as the control group. The severity of the CAD was evaluated using angiographic GS [19]. GS is a highly accepted scoring system for evaluating the coronary atherosclerotic burden. In this scoring system, grading is primarily done according to the narrowing of the lumen of the coronary arteries. For 1% to 25% lumen stenosis 1 point is given, 26% to 50% lumen stenosis 2 points, 51% to 75% lumen stenosis 4 points, 76% to 90% lumen stenosis 8 points,91% to 99% lumen stenosis 16 points and for complete stenosis 32 points. The obtained scores are then multiplied by coefficients representing the importance of the coronary vessel and the segment in which stenosis is present. For the left main coronary artery a coefficient of 5 is used, for the left anterior descending and proximal part of the circumflex coronary artery a coefficient of 2.5 is used and for the proximal right coronary artery a coefficient of 1 is used. Similar coefficients are used for different localizations of the vessels. To obtain the total GS of a patient, the score found for each luminal stenosis and the coefficients are added. After the examination of the patients' medical records, GS was calculated separately for each patient meeting the inclusion criteria. Normal coronary arteries were observed in 42 patients' coronary angiographies (control group). The remaining 152 patients had coronary

lumi nal stenosis (CAD group). The CAD group was divided into two groups according to the severity of atherosclerosis as determined by the GS score. Patients who had GS scores between 1 to 29 were defined as the mild atherosclerosis group (n = 70), and the patients who had GS scores ≥ 30 were defined as the severe atherosclerosis group (n = 82) [20]

STATISTICAL ANALYSIS:

The major parameters of MPV and NLR were analyzed separately. We set α to 0.01 in a one-way analysis of variance power analysis and when the experimental power was above 90%, we terminated the study. According to this, the experimental power for each group (control, mild atherosclerosis, and severe atherosclerosis) with the current patient numbers was enough for the study to have > 90% power. In the study of Kaya et al. [21], a total of 172 patients enrolled and 46 of them constituted the control group. A similar study about the relationship between the NLR and CAD included a total of 175 patients, of which 69 were control group patients with normal coronary arteries [22]. All data was analyzed by using the PASW version 11.5 (SPSS Inc., Chicago, IL, USA).

The normality of the numeric variables was assessed with the Kolmogorov-Smirnov test. The continuous and categorical variables were defined as mean ± standard deviation or median and percentages (%), respectively. The normally distributed numeric variables were compared with an independent sample t test. A chi-square test was used to compare categorical variables. The numeric variables that were not normally distributed were compared with the Mann-Whitney U test. The Kruskal-Wallis test was used to compare the three different groups. Correlation statistics were performed by using the Spearman rank test. A receiver-operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of both MPV and NLR to predictthe presence of severe CAD. A multivariate logistic regression analysis was used to evaluate the independent predictors of severe atherosclerosis. All variables showing significant values less than 0.1 in the univariate analysis (age, sex, DM, high density lipoprotein cholesterol [HDL-C], FPG, WBC, neutrophil, platelet, MPV, and NLR) that were statistically significant in the correlation analysis were included in the multivariate analysis. The significance of all tests was two-tailed and statistical significance was defined as a p value of less than 0.05.

Table1: Baseline charecteristics of control and coronary artery disease group

Variable	CAD (–) (n = 42)	CAD (+) (n = 152)	*p* value[a]
Age, yr	57 ± 11	64 ± 10	< 0.001
Male sex	20 (48)	115 (75)	0.001
Diabetes mellitus	5 (12)	46 (30)	0.028
Hypertension	12 (29)	45 (30)	1.000
Smoking, %	15 (36)	60 (40)	0.792
Dyslipidemia, %	4 (10)	20 (14)	0.713
Systolic blood pressure, mmHg	120 (110–130)	110 (100–120)	0.001[b]
Hemoglobin, g/dL	13.28 ± 1.70	12.90 ± 1.87	0.237
WBC, 10^3/mL	7.74 (6.72–9.35)	7.90 (6.53–9.46)	0.847[b]
Neutrophil, 10^3/mL	4.69 (3.82–5.66)	5.06 (3.97–6.50)	0.137[b]
Lymphocyte, 10^3/mL	2.63 (2.01–2.91)	1.89 (1.43–2.29)	< 0.001[b]
Neutrophil to lymphocyte ratio	2.02 (1.62–2.21)	2.69 (2.17–3.52)	< 0.001[b]
Platelet, 10^3/mL	245 (204–297)	266 (214–312)	0.246[b]
HDL-C, mg/dL	43 (35–50)	36 (32–42)	< 0.001[b]
LDL-C, mg/dL	114 (92–140)	112 (92–141)	0.606[b]
Creatinine, mg/dL	0.78 (0.69–0.86)	0.90 (0.76–1.10)	0.001[b]
FPG, mg/dL	95 (88–118)	107 (94–146)	0.004[b]
eGFR, mL/min/1.73 m^2	92.7 ± 20.1	84.3 ± 22.5	0.030

Table2: Baseline characteristics of gensini score groups

Variable	Mild atherosclerosis (n = 70)	Severe atherosclerosis (n = 82)	*p* value[a]
Age, yr	63 ± 10	65 ± 10	0.272
Male sex	51 (73)	64 (78)	0.580

Diabetes mellitus	15 (21)	31 (38)	0.044
Hypertension	21 (30)	24 (29)	1.000
Systolic blood pressure, mmHg	110 (100–120)	110 (100–120)	0.652[b]
Hemoglobin, g/dL	12.91 ± 1.72	12.89 ± 2.00	0.953
WBC, 10^3/mL	7.57 (6.34–9.31)	8.34 (6.71–10.04)	0.047[b]
Neutrophil, 10^3/mL	4.95 (3.88–5.70)	5.10 (4.02–6.80)	0.149[b]
Lymphocyte, 10^3/mL	1.90 (1.57–2.34)	1.84 (1.37–2.14)	0.070[b]
Neutrophil to lymphocyte ratio	2.53 (1.92–3.42)	2.87 (2.52–3.56)	0.007[b]
Platelet, 10^3/mL	242 (199–295)	274 (231–328)	0.010[b]
Mean platelet volume	9.25 (8.70–9.92)	9.70 (8.90–10.6)	0.005[b]
Platelet distribution width	50.70 (45.62–54.60)	47.05 (43.35–52.85)	0.030[b]
HDL-C, mg/dL	38 (32–45)	35 (32–39)	0.110[b]
LDL-C, mg/dL	108 (88–134)	118 (92–141)	0.323[b]
Creatinine, mg/dL	0.89 (0.76–1.03)	0.93 (0.75–1.11)	0.397[b]
FPG, mg/dL	100 (91–126)	113 (96–165)	0.020[b]
eGFR, mL/min/1.73 m^2	85.74 ± 20.35	83.14 ± 24.28	0.481

Table3: Predictors of severe atherosclerosis in multivariate logistic regression analysis

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Neutrophil to lymphocyte ratio	1.432 (1.075–1.907)	0.014	1.450 (1.080–1.945)	0.013
Mean platelet volume	1.610 (1.152–2.250)	0.005	1.622 (1.147–2.295)	0.006
HDL-C, mg/dL	0.967 (0.928–1.007)	0.105	0.969 (0.929–1.011)	0.145

CI, confidence interval; HDL-C, high density lipoprotein cholesterol

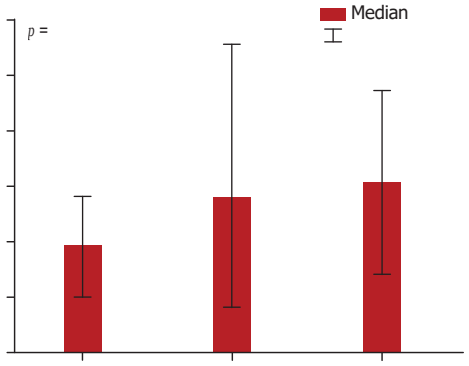

Figure 1:Neutrophil to lymphocyte ratio (NLR) in mem- bers of the control, mild, and severe atherosclerosis groups. aAnalysis of variance test

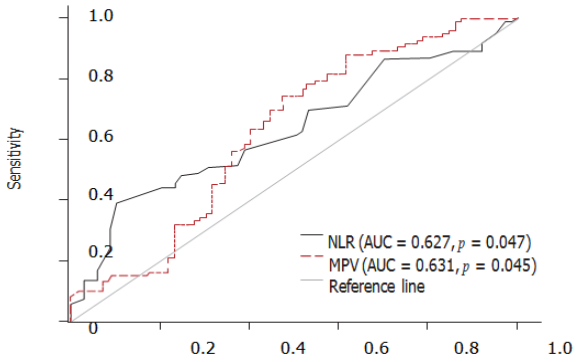

Figure 2:Diagnostic accuracy of neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) in prediction of coronary artery disease. AUC, area under curve

DISCUSSION

In acute coronary syndromes, infl ammation,both local and systemic, plays central role in its pathogenesis. During this infl ammatory process,various hematological parameters release into blood stream, which can be easily measured and are widely availaible. In present study, we studied the relation of various hematological parameters and coronary artery disease severity. Coronary artery disease severity is measured by various scores like, SYNTAX score, TIMI score, GENSINI score etc In this study we revealed that NLR and MPV are independently associated with the presence and severity of CAD. Our study showed that a cut-off value of NLR above 2.54 and a value of MPV above 10.4 can predict the presence of an atherosclerotic process before coronary angiography with quite satisfactory sensitivity and specificity

Recent studies show that LMR can also be used as a marker of inflammation, just like the other markers mentioned above - NLR, MLR. The LMR combines two independent markers of inflammation, and both high monocyte counts and low lymphocyte counts are associated with coronary atherosclerosis [23-25]. Monocytes are recruited in the intima and subintima, differentiate into macrophages and mast cells in response to a number of locally produced cytokines, and initiate the atherosclerotic process by supporting plaque formation [26]. Meanwhile,lymphocytes play an important role in the pathogenesis of atherosclerosis by modulating the immune response, with different subtypes promoting or inhibiting plaque growth and stability. Lymphocytes,especially T cells, play a key role in modulating the immune response in atherosclerotic plaques. Regulatory T cells (Tregs) have been shown to

have anti-inflammatory properties and attenuate atherosclerosis by reducing inflammation in atherosclerotic plaques [27]. The combined role of lymphocytes and monocytes in atherosclerosis highlights the chronic inflammatory process of the disease and may lead to the progression of atherosclerosis [25-27]. So our found decreased LMR, increased MLR in patients with CAD and decreasing LMR and increasing MLR with increasing Gensini score and CAD-RADS group number supplements recent research findings.

Moreover, the relationship between WBC count and CAD severity has been shown by Ates et al. [28]. In a few previous studies, decreased lymphocyte counts were assessed as risk indicators of future cardiovascular events [29]. In our study, NLR incorporated the predictive efficacy of two different WBC subtypes into a single, readily available and easy calculable risk factor. Papa et al. [10] demonstrated NLR as an independent predictor of cardiac mortality and adverse cardiac events in stable CAD patients. The same clinical evidence has been found in acute coronary syndrome patients [30]. Some recent studies revealed the role of NLR as an independent predictor of mortality in coronary intervention planned patients and as a predictor of survival in patients after coronary artery bypass grafting [31]. Similar to our study, Kalay et al. [32] studied the effects of hematologic parameters on the angiographic process of atherosclerosis and found NLR to be a predictor of the progression of atherosclerosis in coronary arteries. The WBC counts were found to be statistically different (p = 0.047) between the groups classified according to GS in our study. In addition, higher levels of the baseline NLR measurement were revealed as an independent predictor of the severity of CAD. The association between inflammatory markers and the extent of the severity of CAD has been known for a long time [33]. Under these circumstances, the association between high levels of WBC count, the consequential high levels of NLR and severe CAD can

be defined by the inflammatory constitution of coronary artery involvement.

Total blood count: leukocytes (neutrophils, lymphocytes, monocytes, eosinophils),erythrocytes, platelets, and mean platelet volume (MPV), and the ratio of these parameters calculated: PLR was calculated by dividing platelet count by lymphocyte count, NLR by dividing neutrophil count to lymphocyte count, NMR as the ratio of neutrophil count to monocyte count and LMR - the ratio of lymphocyte count to monocyte count, MLR by dividing monocyte count to lymphocyte count,while MHR was calculated as the ratio of monocytes to high-density lipoproteins, SIRI was calculated as MLR multiplied by neutrophils and SII was calculated as NLR ultiplied by platelets.

In atherosclerosis,platelets are involved with chemotactic proteins,growth factors and infl ammatory and mitogenic factors. More severe CAD cause the increasing generation of larger platelets with higher MPV from bone marrow. And the large and high amounts of platelets may form atherosclerotic plaques and may lead to the progression of atherosclerosis.[34]

In a study by Altun et al., N/L ratio and high sensitive troponin T were signifi cantly correlated with angiographic severity of ACS as assessed YNTAX score. But in our study, N/L ratio is found to be negatively correlated with coronary artery disease severity. But Trop I and HBA1c was significantly correlated with coronary artery disease severity. A possible hypothesis is being nonspecific nature of hematological markers like white blood cell count, N/L ratio, red cell distribution width.

Mean platelet volume, platelet distribution widthlarge platelet concentration ratio unlike Troponin I.Contrary to some prior studies, MPV was defined as a predictor of severe atherosclerosis in our study [35-36]. Patients with higher MPV levels had high GS and had more severe and critical lesions concurrently. Addi tionally, a correlation ($p = 0.010$) between platelet count and the severity of CAD was observed in this study, in contrast to previous studies [37-38]. The relationship between elevated MPV, platelet counts and the severity of atherosclerosis might be explained by the increase in the metabolic and enzymatic activation of platelets and the increased secretion of mediators from the hemostatically active and larger platelets. In the progression of atherosclerotic lesions, platelets are involved with chemotactic proteins, growth factors and inflammatory and mitogenic factors [39-40]. More severe CAD cause the increasing generation of larger platelets with higher MPV from bone marrow. And the large and high amounts of platelets may form atherosclerotic plaques and may lead to the progression of atherosclerosis.

Studies have shown that immune and inflammatory reactions are closely linked to the development of atherosclerosis [4]. Recently, much attention has been paid to blood cell analysis as a routine laboratory test. Some of the most important cells of the immune system are white blood cells, including lymphocytes, neutrophils, monocytes and macrophages, which play different and important roles in the development of atherosclerosis. For instance, neutrophils can accelerate atherosclerosis at various stages, e.g. by activating macrophages, recruiting monocytes and exerting cytotoxic effects, while lymphocytes modulate the inflammatory response and thus have an anti-atherosclerotic effect [5, 6]. Platelets adhering to the blood vessel wall have been shown to promote leukocyte aggregation and initiate the progression of atherosclerosis before leukocytes penetrate the atherosclerotic plaque [6-7]. Some complete blood count parameters are proven inflammatory biomarkers that predict adverse cardiovascular events. Our results show that increased NLR,as an inflammatory biomarker, contributes to the development of atherosclerosis from initiation through progression. In addition to this, an increased count of platelets with high MPV values furthers the progression of atherosclerotic plaque. This study supports the proven roles of WBC subtypes and platelets in the formation and propagation of atherosclerotic plaque. Patients underwent invasive coronary angiography (CA) or multi-slice computed tomographic coronary angiography (CCTA), or both, to assess coronary artery disease and its severity [30].

The selection of patients from only one hospital may raise a limitation. Additionally, the assessment of the severity of CAD was performed by coronary angiography. Dual-source multi-slice computed tomographic coronary angiography or intravascular ultrasound may be more sensitive in the assessment of the severity of CAD. The other limitation was that we did not measure the synchronous inflammatory biomarkers of the patients.

CONCLUSION

Neutrophil to lymphocyte ratio (NLR) was found to be an independent predictor of severe atherosclerosis. Mean platelet volume (MPV) was found to be an independent predictor of severe atherosclerosis. Cut-off value of NLR above 2.54 and a value of MPV above 10.4 can predict the presence of atherosclerosis before coronary angiography. Both NLR and MPV may be used in daily practice for the prediction and identification of cardiac risks without an intervention. This study revealed the independent predictor roles of both NLR and MPV for the severity of CAD. NLR and MPV are readily available, easy calculable and low priced parameters, unlike other inflammatory markers. Both may be easily used in predicting the severity of CAD before coronary interventions.

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