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ORIGINAL ARTICLE

Can Mean Platelet Volume, Platelet /Lymphocyte ratio and Neutrophil /Lymphocyte ratio predict severity of Coronary Artery calcification assessed by Multidetector CT Coronary Angiography?

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ABSTRACT

Background: Increasing attention is being paid to the role of inflammatory markers and their relationship to the severity of coronary artery disease. Our aim was to prove that simple complete blood count (CBC) indices , platelet / lymphocyte ratio (PLR) , neutrophil / lymphocyte ratio (NLR) and mean platelet volume (MPV) can assess severity of coronary artery calcium using multi detector CT (MDCT). **Methods:** 70 male patients who were scheduled for CT coronary angiography (CTCA) for chest pain or multiple risk factors for coronary artery disease (CAD) were prospectively enrolled. Blood samples for complete blood count, differential leucocyte count and full lipid profile were collected. **Results**: There was a significant negative correlation between NLR ratio and coronary artery calcium score (CACs) (P-value <0.05) and between neutrophil count and number of involved vessels (P-value <0.05). A significant positive correlation was found between MPV, segment involvement score (SIS) and segment stenosis score (SSS) and number of involved vessels (P-value=0.05, 0.01 and 0.01) respectively. Logistic regression analysis showed that PLR and NLR are independent predictors of a calcific plaque (P=0.023 and 0.028) respectively. **Conclusion:** NLR & PLR proved to be good predictors of calcific plaque.

Key words: Mean platelet volume; Platelet/lymphocyte Ratio; Neutrophil/lymphocyte ratio; Coronary artery disease; Multi detector computed tomography angiography.

INTRODUCTION

Several mechanisms are involved in initiation and perpetuation of atherosclerosis, inflammation is a very important one. Therefore, the role of inflammatory markers and their relationship to the severity of coronary artery disease is gaining increasing attention [1].

Many techniques have been studied to assess inflammation, the simpler being systemically measuring inflammatory markers including number of neutrophils, lymphocytes, total platelet count and mean platelet volume. The more sophisticated techniques include imaging, temperature calculation and assessment of heterogeneity of pH [2]. One of the latest non-invasive methods used in assessment of extent of coronary artery disease is multidetector computer tomography (MDCT), which has demonstrated high sensitivity (85-95%) and specificity (95-98%) in the diagnosis and assessment of severity of CAD .Thus, it is now considered as an invasive coronary angiography gatekeeper [3]

MDCT describes the degree of luminal narrowing; the number of vessels affected and further determines the form of plaque and the calcium score of the coronary artery (CACs) [4]

METHODS

Written informed consent was obtained from all participants, the study was approved by the

research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. From a group of patients referred to the Cardiology Department at Zagazig University Hospitals and Kobry Elkoba hospital for MSCT coronary angiography during a 6 month period (between January and May 2020) for suspected cardiac symptoms (typical or atypical chest pain or dyspnea on exertion, or equivocal stress test results along with standard cardiac risk factors, a total of 120 patients were reviewed for inclusion in our study. Patients with evidence of prior significant CAD determined as follows: previous coronary angiography showing coronary artery stenosis >50% (n=10) prior percutaneous intervention (n=10) or prior coronary artery bypass grafting (n=10) Patients presenting to the emergency department with acute chest pain were not included (n=10). Patients with incomplete electronic medical records or a non-coronary indication for MSCT were also excluded (n=10). Thus we were left with 70 male patients who were prospectively enrolled.

Clinical characteristics, lipid parameters and laboratory test information of the study patients were collected. Family history of premature CAD was defined as CAD in first-degree male relatives ≤ 55 years of age or female relatives ≤ 65-year-old.

Neutrophil count, neutrophil lymphocyte ratio, platelet count, platelet /lymphocyte ratio , mean platelet volume, total cholesterol, triglycerides , low density lipoprotein (LDL) and high density lipoprotein (HDL).. White blood cell differential counts were determined in whole blood by ABX Pentra XL80 (HORIBA Medical) and SYSMEX XT.1800i devices using flow cytometry

The CTCA was performed using a Siemens Definition flash 128 dual-source with the following scan parameters: 64 × 0.6 mm collimation, tube voltage of 120 kV, gantry rotation time of 330 ms, and tube current of 770–850 mA. For the contrast-enhanced scans, in each patient 60 mL of iodinated contrast followed by 60 mL of saline solution was injected.

All patients received 5 mg of bisoprolol orally before the computed tomography (CTCA) scan, and patients with a heart rate >70 beats/min received 2 mg of metoprolol intravenously. In addition, patients received 0.5 mg of sublingual nitroglycerin.

The modified 17-segment American Heart Association (AHA) model for coronary segment classification was used for assessment of the coronary circulation and is shown in table 1 [5] Coronary atherosclerotic plaques were defined as a tissue structure >1 mm2 detected within coronary vessels **[6]**

The severity of luminal-diameter stenosis was visually divided into (i) <50% luminal stenosis, (ii) 50–69% luminal stenosis, or (iii) >70% luminal stenosis.

Axial and multi-planar reconstruction images were used to determine the degree of luminal stenosis, this was estimated using proximal and distal reference segments. We used the most adjacent points to the maximal stenosis at which there was minimal or no plaque to be our reference segment .We classified plaque types into 3 types based on plaque density and degree of calcification : (i) non-calcified plaque = plaque with lower density compared with the contrast-enhanced vessel lumen without any calcification (>150 HU), (ii) calcified plaque = plaque with predominantly calcification, or (iii) mixed plaque = plaque with a small amount of calcification elements within a single plaque. **[6]**

All images were interpreted by 2 experienced readers intermediate or borderline lesions were reassessed for the consensus judgment**. [7]**

Assessment of Severity & extend of CAD burden was done using, CACs, SSS, SIS, luminal-narrowing and type of plaques by the following protocol:

Coronary calcium scanning score: Agatston score was used to calculate amount of calcium. For each artery, each calcification, or the entire heart—sometimes called total calcium score (TCS)—are calculated by summing the respective values for the regions of interest. **[5]**

Segment Stenosis Score (SSS): the model is based on the AHA segmentation published in 1974 shown in **Figure 1 [8]**

Segment Involvement Score (SIS):SIS is shown in **figure 2**; it was used as a quantifying measure of coronary plaque. Presence of a plaque is given score 1 while absence is given a score 0. The sum of all involved segments (ranging from 0 to 16) was calculated for each patient **[9]** (See figure 2)

Statistical analysis:

All analyses were performed using the SPSS for Windows 20.0 software package. Continuous variables were presented as mean standard deviation. Categorical variables were presented as percentages. All data were tested for normal distribution with the Kolmogorov-Smirnov test. The chi-square test, one-way ANOVA, and student test were used to test for differences in categorical variables. Pearson's and Spearmen's correlation exponents were used to force of relationship between continuous variables. Independent predictors where identified using a Multivariate logistic regression model.

RESULTS

Table 2. demonstrated all the basic demographic, and CBC findings of the study group .The study patients were all males whose mean age was 56.9 ± (10.3) years . ***We found a*** significant negative correlation between NLR and CACs (P-value <0.05), similarly, a negative correlation was also found between neutrophil count and number of involved vessels (P-value <0.05 .Furthermore, a significant positive correlation was seen between MPV and SIS, SSS and number of involved vessels (P-value= 0.05, 0.01and 0.01) respectively. Total cholesterol was seen to be positively correlated to CACs (P-value = 0.01) while high density lipoprotein (HDL) was negatively correlated to number of involved vessels (P-value = 0.01). These findings were presented in **table 3, figures 3, 4 and 5.**

Table 4. shows multivariate logistic regression analysis of the different CBC variables. Amongst all CBC parameters tested, PLR and NLR were found to be independent predictors of calcific plaque (P=0.023 and 0.028) respectively.

Table 1. Coronary artery anatomy using a 17-segment model

Vessel name	Segment no, Segment name
Right coronary artery (RCA)	**1 Proximal right coronary** **2 Mid right coronary** **3 Distal right coronary** **4a Posterior descending artery** **4b Right postero-lateral branch**
Left main coronary artery(LM)	**5 Left main coronary artery**
Left anterior descending artery (LAD)	**6 Proximal left anterior descending** **7 Mid left anterior descending** **8 Distal left anterior descending** **9 First diagonal branch** **10 Second diagonal branch**
Left circumflex artery (LCX)	**11 Proximal left circumflex** **12 First (obtuse) marginal** **13 Mid left circumflex** **14 Second (obtuse) marginal** **15 Distal left circumflex**
Intermediate branch	**16 Intermediate branch**

Table 2: Baseline characteristics of the study population

Variable	Value
Age (mean ± SD)	56.97 ±10.3.
Smokers N (%)	40 (57%)
HTN N (%)	31 (44%)
DM N (%)	15 (21%)
Smoking N (%)	44 (63%)
Hyperlipidemic N (%)	35 (50%)
WBCs (mean ± SD)	7.5 ± 2.4
MPV (mean ± SD)	10.37 ± 1.2
Platelet count (mean ± SD))	223 ± 58
Neutrophil count (mean ± SD)	53.4 ± 11.9
Lymphocytes (mean ± SD)	35.4 ±11.1
NLR	1.7 ±0.8
PLR	6.9 ± 3.4
Monocytes (mean ± SD)	9.09 ± 4.5
Esinophils (mean ± SD)	3.46 ±2.4
Basophils (mean ± SD)	0.42 ± 0.4

Table 3: Correlation between different coronary angiography scores by MSCT and CBC indices

	SSS		SIS		CACS		No.Involved Vessels	
	R	**P-value**	**r**	**P-value**	**R**	**P-value**	**R**	**P-value**
N/L ratio	-0.15	0.31	-0.15	0.31	-0.29	0.03*	-0.22	0.09
Neutrophil %	-0.06	0.70	-0.09	0.52	-0.10	0.48	- 0.27	0.04*
P/L ratio	-0.07	0.66	-0.09	0.52	-0.11	0.42	-0.13	0.34
MPV (fl)	0.28	0.05*	0.33	0.01*	-0.21	0.13	0.32	0.01*
Total cholesterol, mg/dL	0.13	0.37	0.15	0.30	0.36	0.01*	0.16	0.23
HDL, mg/dL	0.14	0.36	-0.02	0.90	-0.11	0.47	-0.33	0.01*

* indicate significant difference (P<0.05).
[(a)]SSS=segment stenosis score [(b)]SIS=segment involvement score [(c)] CACs=coronary artery ca^{2+} score [(d)]MPV=mean platelet volume;

Table 4. Logistic regression analysis to determine predictors of a calcified plaque

Variable	Estimate	St. error	P-value
HTN	2.171061	1.249048	0.0822
PLT/L ratio	0.005650	0.002498	0.0237
N/L ratio	-0.033920	0.015444	0.0281
LDL	0.007466	0.004344	0.0857

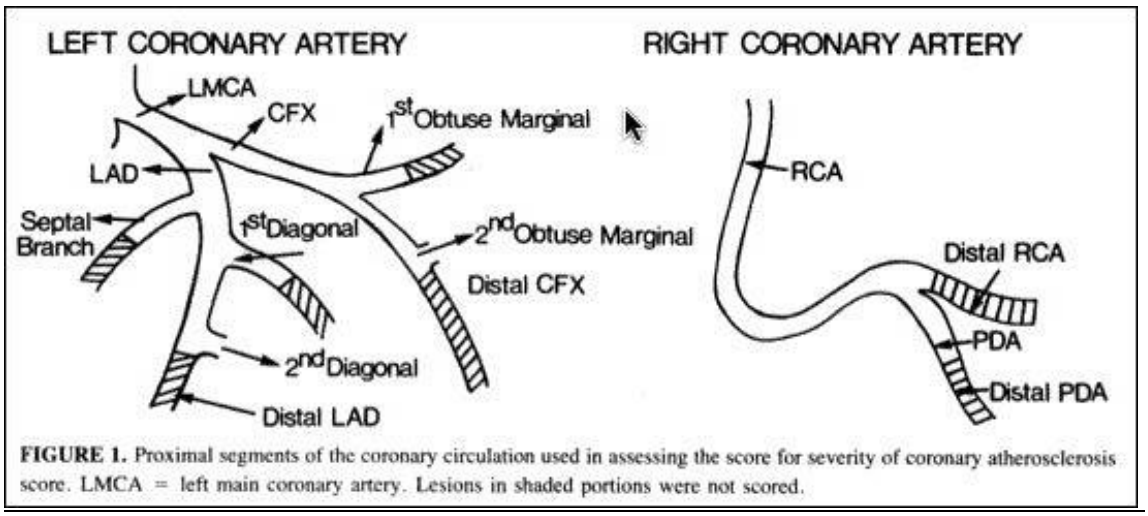

FIGURE 1. Proximal segments of the coronary circulation used in assessing the score for severity of coronary atherosclerosis score. LMCA = left main coronary artery. Lesions in shaded portions were not scored.

Figure 1. Segment stenosis score assessment; segmentation is based on the AHA segmentation published by" Austen et al.1974"

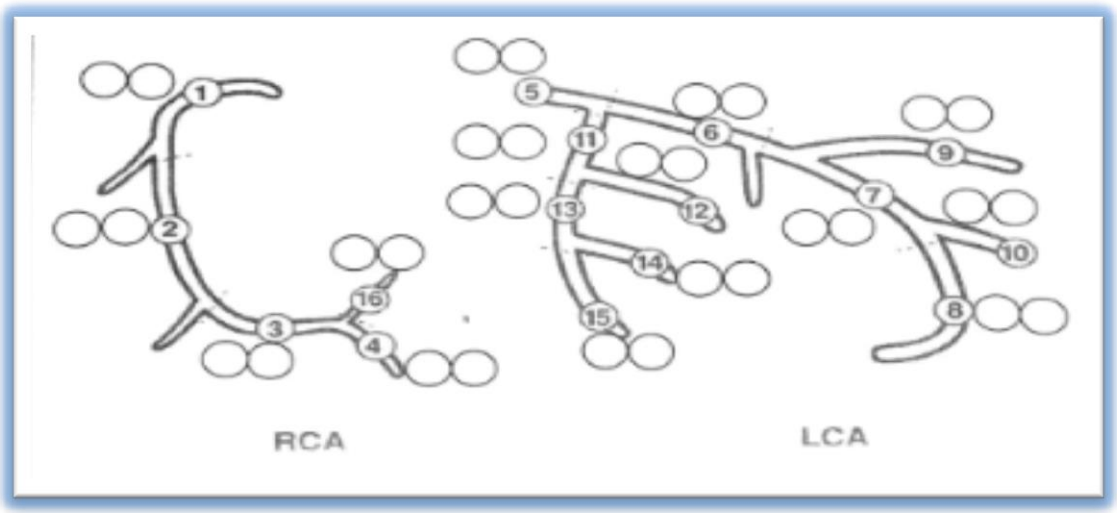

Figure 2. assessment of segment involvement score

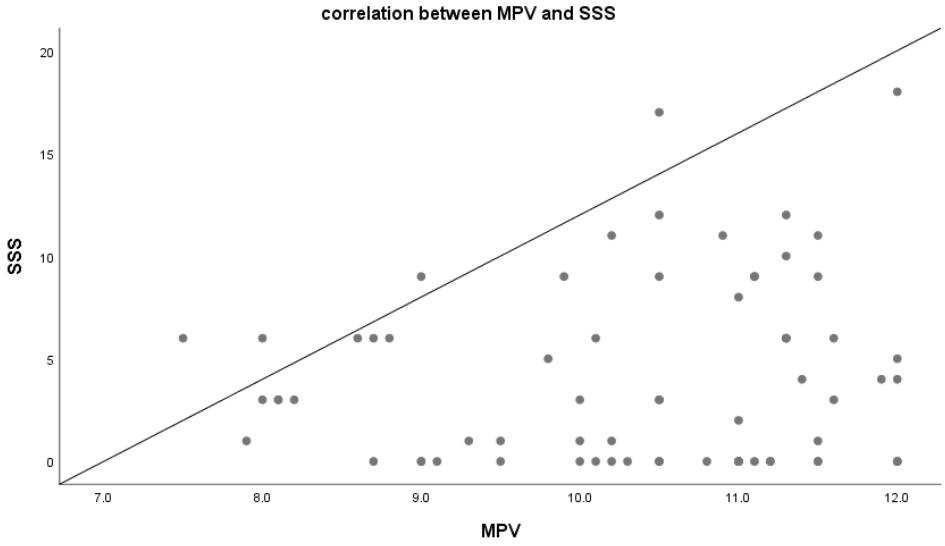

Figure 3. Correlation between MPV and SSS

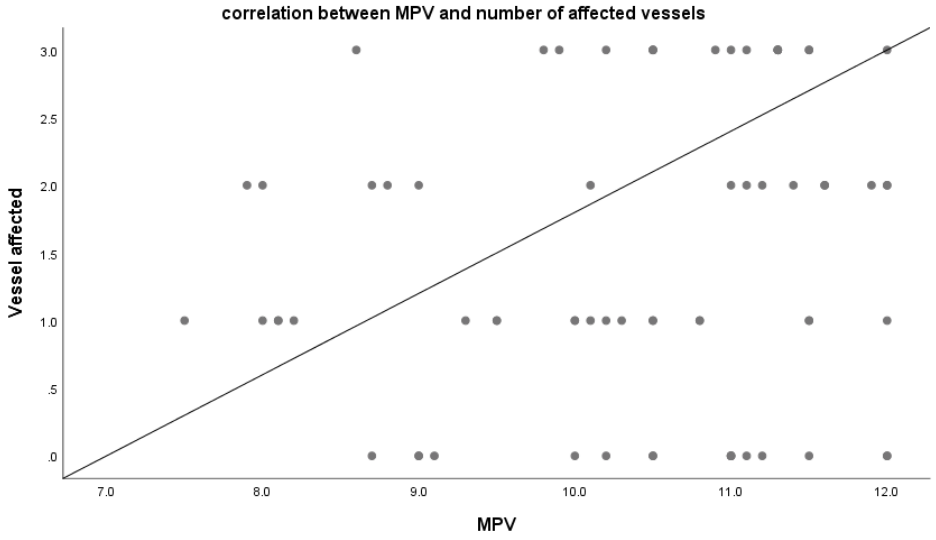

Figure 4. Correlation between MPV and number of affected vessels

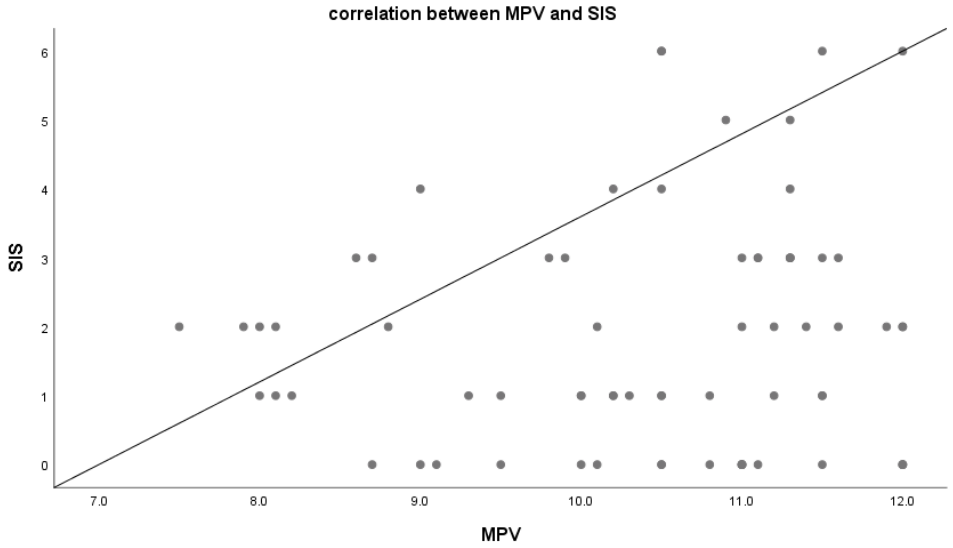

Figure 5. Correlation between MPV and SIS

DISCUSSION

There are minimal data on contemporary management and outcomes of MSCT identified inflammatory cell markers such as neutrophil, lymphocyte, platelet and MPV and their association with various plaque forms (calcific, mixed and non-calcific) [11].

CBC indices and MDCT scores: A univariate correlation model between CT scores (SSS, SIS and CACs) and CBC indices showed a significant negative correlation between NLR and CACs. This result was in concordance with Nilsson and colleagues [12]**,** they described correlations between neutrophil counts and neutrophil/lymphocyte ratios with plaque composition on CT coronary angiography (CCTA). NLR was considered the main marker of inflammation and atherosclerosis process and it has been associated with the presence, severity and progression of coronary atherosclerosis as assessed by various modes of coronary imaging. Similarly, MPV (mean platelet volume) was positively correlated with SSS (Segment Stenosis Score), SIS (Segment Involvement Score) and number of involved vessels (P value 0.05, 0.01 and 0.01) respectively. These results agreed with Hamur and colleagues [13]and Uysal and colleagues [14] in both studies patients with higher MPV levels had high Gensisi Score and had more severe and critical lesions .

Our results were also concordant with ***Gurses*** and colleagues [15], they retrospectively analyzed 684 patients without a previous history of coronary artery disease (CAD), in whom dual source 64-slice computed tomography angiography (CTA) was performed due to suspicion of CAD. They found a 30 % prevalence of critical coronary plaques amongst the study population and in this group MPV was found to be significantly higher.

The behavior of larger platelets was explained by Adel and colleagues [16]. They found these thrombocytes to be more active both enzymatically and metabolically than small platelets. They also have higher levels of thromboxane A2 , increased intracellular and surface procoagulant protein ,their receptors have more adhesion properties and thus they have more prothrombotic properties . Furthermore, larger platelets are released from the marrow as smaller ones are consumed in atherosclerotic plaques. Adel and colleagues [16] found a positive correlation between PLR and NLR ratio in the presence of calcific plaque in multivariate logistic regression analysis (p value 0.02). This result was in concordance with Akdag and colleagues [13] who studied the relation between PLT/L ratio and calcific Aortic Stenosis and concluded that PLR was positively associated with calcification.

Several studies including Ommen and colleagues [17] reported that decreased lymphocyte count was significantly associated with survival in patients with stable coronary artery disease and it had a potential independent prognostic value for these patients.

The role of platelets includes mobilizing both leukocytes and progenitor cells into sites of vessel injury. Furthermore, they are capable of moving anti-inflammatory and pro inflammatory micro particles into the blood stream. Higher number of platelets and lower lymphocytes have both been accused of enhancing progression of atherosclerosis and development of acute coronary events. Thus PLR combined the predictive risk of both platelets and lymphocytes and thus was described as a prognostic marker to development of acute cardiac events. A study by Kurtul and colleagues [18] showed an association between PLR and CRP, furthermore they found that PLR can be used as a predictor of no reflow after ST-elevation myocardial infarction (STEMI).

Correlation between Total cholesterol and CACS: We also found a significant positive correlation between serum total cholesterol and the degree of calcification detected using the Agatson score, ($P < 0.01$) .

Elevated levels of cholesterol particularly LDL cholesterol has been found to have a critical role in the development of atherosclerosis and was strongly associated with coronary heart disease (CHD) risk. [19] This finding was supported by the results of Kronmal and colleagues [20] in the MESA cohort, which studied the cardiovascular risk factors associated with both the risk of developing incident coronary calcium and increases in existing calcification.

While HDL had negative correlation with number of involved vessels P value 0.01 this result is dis-concordant with Harada and colleagues [21] where HDL had no significant value to number of involved vessels in the three classified groups. We can explain our results however as HDL has anti-atherogenic properties including its mediation of reverse cholesterol transport, in which cholesterol from peripheral tissues is returned to the liver for excretion in the bile it is also known to have antioxidant activity and has a pro-vital role as protective factor in atherosclerosis. [22]. This is a single center study with a relatively small sample size ,larger multicenter studies are needed to confirm and validate these results.

CONCLUSION

This research highlights the role of three CBC indices in determining CAD severity and the existence of atherosclerotic plaques. N / L ratio and PLR are strong calcific plaque predictors while MPV has a positive association with SSS, SIS and number of segments involved.The use of these CBC indices as simple, cost effective parameters to predict type of plaque and plaque vulnerability might aid in risk stratifying patients. Furthermore, detection of multiple calcific plaques necessitates lesion preparation before PCI procedures.

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