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Relation of neutrophil-to-lymphocyte, platelet-to-lymphocyte ratio and CRP level with coronary artery disease severity in patients undergoing coronary angiography

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Abstract

Background: coronary artery disease (CAD) is the leading cause of morbidity and mortality throughout the world. It has a complex pathophysiology, and inflammation seems to play an important role in CAD**.** Previous studies have shown that higher levels of inflammatory markers are associated with the severity of CAD and worse cardiovascular outcome. Although endothelial damage has been known as the triggering factor for the formation of atherosclerotic plagues, inflammatory process is responsible in the initiation and progression of the atherosclerosis. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as new predictors for worse cardiovascular outcome. Previous studies have shown that NLR is associated with morbidity and mortality in many cardiovascular diseases such as hypertension, heart failure, infective endocarditis, and acute coronary syndromes (ACS).

Aims: The aim of this study was to explore the relation of NLR , PLR and CRP level with severity of coronary artery disease (CAD) using the Syntax score (Sxscore).

Patients and Methods: This study was conducted to investigate the relationship between the severity of coronary artery disease and inflammatory markers (lymphocyte ratio, lymphocyte platelet, CRP) by sytax score in patients undergoing elective coronary angiography, the active number of 100 patients with a chronic stable was taken Coronary angiography, different markers for coronary assessment, renal function tests, INR, ECG and Echocardiography. A complete clinical evaluation was performed for each of our patients

Results: Coronary lesions were evaluated by the result of camel synthesis and there was a strong relationship between NLR, PLR, CRP level, and coronary heart disease r. 526 p 0.001, r 0.317 p 0.001, r 0.699 p 0.001 However, when we divided the patient for a result Syntax The results show some difference in determining who are drafting the sentence above 21, we found a negative relationship between NLR, PLR and syntax points, while the CRP level was positively correlated at the level of the structure below 31 a significant negative correlation was found with the construct conclusion above 31.

Conclusion: Our study concluded that the severity of coronary artery disease is associated with NLR, PLR, CRP levels to some extent in the patient with angina for chronic stable chest.

Keywords: CAD, NLR, PLR, CRP, Syntax score

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality throughout the world. It has a complex pathophysiology, and inflammation seems to play an important role in CAD **(1)**.

Previous studies have shown that higher levels of inflammatory markers are associated with the severity of CAD and worse cardiovascular outcome**(2)**.

Although endothelial damage has been known as the triggering factor for the formation of atherosclerotic plagues, inflammatory process is responsible in the initiation and progression of the atherosclerosis **(1).**

Inflammatory markers, including white blood cell (WBC), C-reactive protein (CRP), and homocysteine, have been used for the prediction of cardiovascular events in asymptomatic patients **(3).**

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as new predictors for worse cardiovascular outcome**(4).**

Previous studies have shown that NLR is associated with morbidity and mortality in many cardiovascular diseases such as hypertension, heart failure, infective endocarditis, and acute coronary syndromes (ACS) **(5).**

Although previous data have shown that NLR is associated with severity of CAD **,**its relation with PLR remains unclear.CRP which is a hepatically derived pentraxin, composed of five 23kDa subunits, and has a critical role in innate immune response**(6)**. Hs-CRP has known

as a marker for low grade systemic chronic inflammation, and is directly involved in the endothelial dysfunction, platelet aggregation and atherosclerosis. This protein has been shown to have prognostic value in patients with acute coronary syndromes (ACS) and plays different roles in pathogenesis of atherosclerosis[7].

Aim of the work:

The aim of this study is to explore the relation of NLR , PLRand CRP level with severity of coronary artery disease (CAD) using the SYNTAX score (Sxscore).

Patients and Methods:

Study Design: Cross sectional, descriptive study

- **Background and Demographic Characteristics**

Inclusion criteria:

Patients were included in the study if they fulfilled the following criteria:

- Typical chest pain.
- Significant ischemic ECG changes.

Exclusion criteria

- Congestive heart failure.
- Any systemic infection.
- Chronic obstructive pulmonary disease.
- Chronic kidney disease.
- Chronic inflammatory disease.
- Heamatopoitic system disorder
- Malignancy.

- **Methodology:**
  - 100 consecutive patients were selected among patients with CAD undergoing coronary angiography in the catheterization laboratory in Naser Institute Hospital.
  - **All subjects** were **subjected to the following:**
- ***Clinical evaluation:***
  - Age and gender.
  - Risk factors (smoking status, diabetes mellitus, hypertension, dyslipidemia).
  - Full clinical examination.
  - Resting electrocardiography .
- **Laboratory investigation:**
  - Coronary angiography and assessment of severity of CAD using SX score.
  - Complete blood count with differential count in order to obtain NLR(total leucocytic count and its subtypes), PLR. Biochemical values will be measured from blood samples and analysed using Beckman Coulter device.
  - CRP level.
  - Renal function test:
    - Serum creatinine.
    - Serum urea.
    - BUN.
- ***Possible Risk***

Contrast agent hypersensitivity(reaction to contrast agent).

- Radiation exposure.
- Mortality

- ***Primary outcome parameter***
  - SYNTAX score.
  - Platelet to lymphocyte ratio (PLR) .
  - CRP level
  - Neutrophil to lymphocyte ratio (NLR).
- **Sample size:**
  - The study was conducted on 100 patients of both genders and different ages admitted to the coronary care unit at Nasser institute and diagnosed with CAD after fulfilling the inclusion and exclusion criteria.

Statistical analysis:

- Data analysis was performed using descriptive statistics and correlation analysis; all numerical data were expressed as mean and standard deviation. Tests of normal distribution were done to select the appropriate statistical tests (parametric Vs non –parametric), Correlation analysis was done.
- **Source of funding:** Self funded.

Time plan: 6 months were expected for the cases collection, their screening and the review of literature to be done, 1 more month was spent in the statistical analysis of the collected data and test results as well as discussion writing & two more months are estimated for publishing the final result.

Ethical Committee approval: Approval was obtained from research committee in our department and also from the patients included in the study for sampling and using their personal data .

Results

1- Age distribution:

In the studied population the age has ranged from 39 to 73 years and the mean age was 58.15 ± 8.15 years.

2- Risk factors:

❖ ***Hypertension:***

In this study sixty four (64%) patients of the total number were hypertensive, while thirty six (36%) were non hypertensive as shown in table 1

Table (1):Distribution of hypertension in the studied population

Hypertension	No (%)
Hypertensive	64 (64%)
Non- Hypertensive	36 (36%)
Total	100 (100%)

❖ ***Diabetes mellitus:***

Forty four (44%) patients in the studied population were diabetic. While, fifty six (56%) patients were not-diabetic .

Table (2): Distribution of diabetes mellitus in the studied population

Diabetes mellitus	No (%)
Diabetic	44 (44%)
Not- Diabetic	56 (56%)
Total	100 (100%)

❖ ***Smoking:***

In the studied population twenty eight (28%) patients of the total number were smokers while the remaining seventy two (72%) were nonsmokers as shown in table 3

Smoking	No (%)
Smoker	28(28%)
Nonsmokers	72 (72%)
Total	100 (100%)

❖ **Dyslipidemia**

In the studied population sixty three (63%) patients of the total number were dyslipidemia, while thirty seven (37%) were none,

Table (4):Distribution of dyslipidemia in the studied population

Dyslipidemia	No (%)
No	63 (63%)
Yes	37 (37%)
Total	100 (100%)

Table 5: Laboratory data in the study

Parameter	mean±SD
neutrophil	4199.76±1657.03
lymphocyte	2166.65±891.75
WBCs	6.65±2.30
platelet	325073.88±15300.5
CRP	4.49±2.41
neutro/lymph	2.02±0.56
platlet/lymph	153.63±50.15

Mean WBCs count in our patients were 6650 ±2300, mean neutrophil count were 4199.76±1657.03, mean lymphocytes were 2166.65±891.75, platelets 325073.88±15300.5, mean CRP level 4.49±2.41, mean neutro/lymph ratio 2.02±0.56, platelet/lymph 153.63±50.15.

❖ **Blood vessels**

In the studied population twenty one (21%) patients of the total number had 0 vessel, forty four (44%) had single vessel, twenty one (21%) patients of the total number had 2 vessel and fourteen (14%) patients had 3 vessels and more (X^2= 20.560 & P=0.001).

Table (6): Number of blood

Vessels	No (%)
0	21 (21%)
1	44 (44%)
2	21 (21%)
3	14 (14%)
Total	100(100%)

Table (7): Correlation between syntax and other parameters in 3 divided groups

Syntax	Group 1 Syntax< 21	Group2 Syntax 21-31	Group3 Syntax> 31
Neutrophil/lymph Mean ±SD r P	1.99±0.55 0.434 0.001**	2.67±0.32 -0.062 0.847	1.94±0.25 -0.989 0.001**
Platelet/lymph Mean ±SD r P	154.35±50 0.395 0.001**	167±50.98 -0.299 0.345	117±35.15 -0.981 0.001**
CRP Mean ±SD r P	4.391±2.44 0.522 0.001**	5.8±1.37 0.648 0.023*	6.33±0.9 -0.264 0.492

Correlation according syntax index and other parameters

Table (7) showed the following significant correlations between syntax and studied parameters, we have subdivided the studied population into three groups according to the value of syntax and the decision dependent the sx below 21 which favors PCI while the one above 31 favors CABG and the gray zone in between was our third group the we have

studied the relation between these groups and the inflammatory markers NLR ,PLR ,CRP

- ❖ Syntax **<21**
  - A positive correlation was found between Syntax **<21** and neutrophil/Lymph (r=0.434 & P<0.001).
  - A positive correlation was found between Syntax**<21**and Platlet/Lymph (r=0.395 & P<0.001).
  - A positive correlation was found between Syntax **<21**and neutrophil/Lymph (r=0.522 & P<0.001).
- ❖ Syntax **21-31**
  - Non-significant negative correlation was found between Syntax **21-31** and neutrophil/Lymph and Platlet/Lymph.
  - A positive correlation was found between Syntax **21-31**and CRP (r=0.648 & P<0.023).
- ❖ Syntax **>31**
  - A negative correlation was found between Syntax**>31** and neutrophil/Lymph (r=0.989 &P<0.001).
  - A negative correlation was found between Syntax**>31** and Platlet/Lymph (r=-0.981 &P<0.001).
  - Non-significant negative correlation was found between Syntax**>31**and CRP (r=-0.264 &P<0.492). **Table (8): Comparison between parameters according to syntax score**

group	Syntax< 21(79) mean±SD	Syntax 21-31(12) mean±SD	Syntax> 31(9) mean±SD	p
Neutrophil /lymph	1.99±0.55[a]	2.67±0.32[b]	1.94±0.25[a]	≤0.001
Platelet/lymph	154.35±50[a]	167±50.98[a]	117±35.15[b]	0.025
CRP	4.391±2.44[a]	5.8±1.37[a]	6.33±0.9[b]	≤0.01

Different letters means mean significant at p <0.05

Similar letters means mean insignificant at p <0.05

As illustrated in table (8); there was highly significant difference between parameters according to syntax score.

Mean NLRis near equal in groups syntax<21 and syntax >31while the group in the middle shows some difference.

Mean PLR show lesser level at the group of patients with syntax >31, while mean CRP level shows higher levels at this group.

Correlation between syntax and other parameters

Table (9): showed the following significant correlations between syntax and studied parameter:

- A positive correlation was found between syntax and neutrophil/Lymph (r=0.526 &P<0.001). fig 1
- A positive correlation was found between syntax and Platlet/Lymph (r=0.317 &P<0.001). fig 2
- A positive correlation was found between syntax and neutrophil/Lymph (r=0.736 &P<0.001). fig 3

Table (9): Correlation between syntax and other parameters

	Syntax
Neutrophil/lymp	
r	0.526
P	0.001**
Platelet/lymph	
r	0.317
P	0.001**
CRP	
r	0.699
P	0.001**

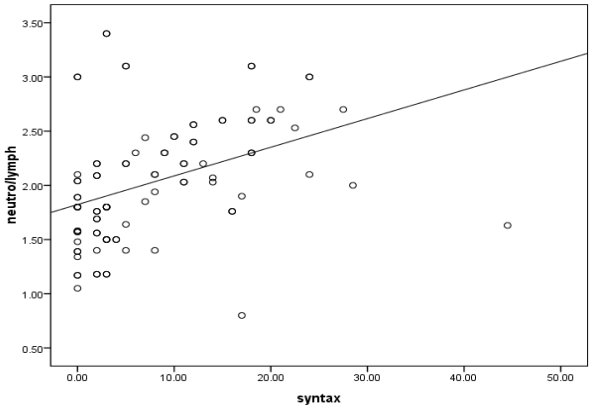

Fig (1): Correlation between syntax and neutrophil/Lymph.

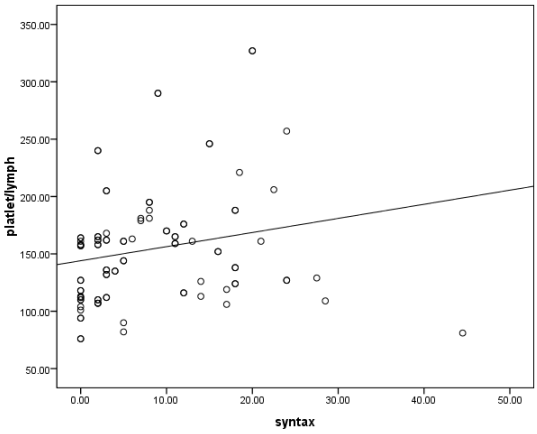

Fig (2): Correlation between syntax and platelet/Lymph.

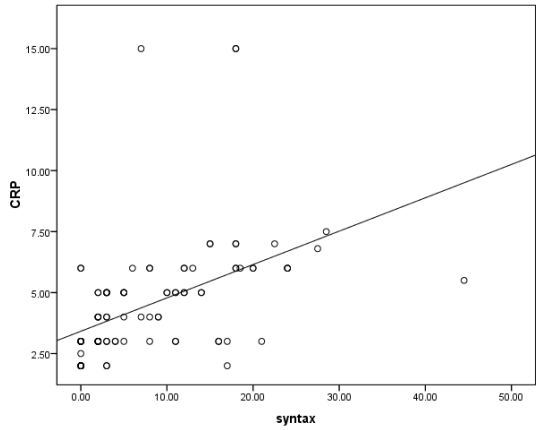

Fig (3): Correlation between syntax and CRP.

Discussion

Cardiovascular diseases (CVDs) are still the leading cause of death all over the world, despite modern therapeutic advances. It is known that inflammation plays a substantial role in the initiation and propagation of the complex atherosclerotic process that lies beneath CVD. The role of inflammation in CVD has been studied extensively, and a consistent relationship between various inflammatory markers and CVD has been established in the past **[8].**

A low blood lymphocyte count has been shown to be related with worse cardiovascular consequences in patients with CAD and chronic heart failure **[9].** In cases of sustained inflammation, lymphocyte counts decrease due to increased lymphocyte apoptosis.

Lymphocytes represent a more convenient immune response, while neutrophils cause a destructive inflammatory reaction. Also, ongoing inflammatory conditions lead to increased proliferation in megakaryocytic series and relative thrombocytosis. The development and progression of atherosclerosis is a multifactorial process. Inflammation plays a major role at all stages of atherosclerosis from initiation through progression and finally in the thrombotic complications of this disease. White blood cell count and its subtypes have been investigated as inflammatory biomarkers to predict future adverse cardiovascular events **[10].** Increased number of circulating neutrophils and decreased lymphocytes are risk indicators of future cardiovascular events**[11]**.

Elevated NLR integrates the predictive risk of these 2 leukocyte subtypes into a single risk factor **[12]**.

Several studies have shown a relationship between NLR and CAD. It has been shown that NLR measured on admission was an independent predictor of adverse cardiac events in patients with ACS and stable CADs **[13]**.

Gibson *et al.* **[24]** has shown that NLR associated with a poorer survival after CABG. Similarly, **Duffy *et al.*** **[14]** showed that pre-procedural NLR was an independent predictor of all-cause death in patients undergoing percutaneous coronary interventions.

Horne *et al.* **[10]** demonstrated that NLR was confirmed to be an independent predictor of death/myocardial infarction in patients with CAD. **Kalay *et al.*** **[15]** investigated the determinants of progression of coronary atherosclerosis and showed NLR as a predictor of progression**.**

In the present study, we are going to demonstrate the relation between various inflammatory markers and severity of coronary artery disease using syntax score.

The first para meter included in our study isneutrophil lymphocyte ratio, and there were appositive correlation between NLR and severity of coronary artery disease (r=0.526 & P<0.001). which were measured using syntaxscores in patients undergoing elective coronary angiography specially in patients with syntax score less than 21 (r.434, p 0.001) while a negative correlation was found at higher levels of syntax more than 31 (r-989, P 0.001), and a less negative relation in between 21_31 (r-0.062 ,P 0.847).

The second parameters we searched for its predictive value of CAD severity was platelet lymphocyte ratio:

Previous studies demonstrated an association between high circulating platelet count and major adverse cardiovascular outcomes in patients with coronary artery disease (CAD) and also in healthy adults **[16].**

Platelet- lymphocyte ratio (PLR) is a new prognostic marker that integrates the risk prediction of these 2 parameters into 1. It gives an idea about both the aggregation and inflammation pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden. PLR was found to be useful in predicting poor prognosis in cancer population [(17)] and in predicting critical limb ischemia in peripheral artery disease previously [(18)].

In line with these findings, a high PLR tertile of a recent study population that presented with STEMI showed poorer outcomes compared to the low PLR group, and PLR was found to be an independent predictor of in-hospital mortality in patients with STEMI [(19)].

Our study aimed to detect the usefulness of a recently defined cardiovascular risk marker, PLR, in predicting the severity of coronary atherosclerosis, and there was appositive correlation between PLR and severity of CAD (r=0.317 &P<0.001).differs from one group to the other at syntax score less than 21 there was appositive correlation between PLR and syntax score (r=0.395 &P<0.001) while a negative correlation was found in patients with syntax above 31 (r=-0.981 &P<0.001) and a less negative correlation in the intermediate group syntax 21_31(r -0.299 P .345).

During the past decades a great deal of knowledge concerning the pathophysiology of CHD has been achieved, and age (older than 40 years for men, 45 years for women), male sex, family history of CHD, smoking, hypertension, diabetes, obesity, high total cholesterol, low high density lipoprotein cholesterol (HDL-C), high low density lipoprotein cholesterol (LDLC), high triglycerides, low physical activity, and accumulation of abdominal fat are some of the major risk factors[(20)]. However, despite identification of important risk factors, CHD remains the leading cause of death worldwide. Up to half of all events associated with CHD are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors, including dyslipidemia. As a result, attention has increasingly turned to the role of other factors, such as inflammation, in the development of atherosclerosis and CHD[(21)].

Among them, C-reactive protein (CRP), a prototype marker of the inflammatory process, is the most studied both as a causal factor and in the prediction of CHD [(21)].

CRP is the forerunner in the hunt for inflammatory markers and is subject to intensive research in numerous studies worldwide. Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of CHD [(22)].

Multiple prospective cohort studies have established that increased CRP levels are associated with increased CHD risk in both genders, across a wide age range, and in primary as well as secondary prevention settings. These findings have been consistent in different populations with diverse ethnic backgrounds and in diverse clinical settings, and they have predicted risk of a variety of cardiovascular outcomes, including incident acute myocardial infarction (AMI), stroke, sudden cardiac death, peripheral artery disease and also incident diabetes and new onset hypertension. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndrome(ACS) [(23)].

In our study we have assessed CRP level in all patients with chronic stable angina undergoing elective coronary angiography and we have studied the relation between CRP level and severity of CAD as assessed by syntax score ,there was a significant correlation between CRP level and syntax score (r.699, P 0.001)

Conclusion:

Our study concluded that the severity of coronary artery disease is associated with NLR, PLR, CRP levels to some extent in the patient with angina for chronic stable chest.

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