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Research Article

Neutrophil-Lymphocyte Ratio and Coronary Artery Disease Risk in Patients Undergoing Coronary Angiography

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Abstract

Introduction: Inflammatory response is one of the main mechanisms in the pathogenesis of atherosclerosis and its progression. The neutrophil-lymphocyte ratio (NLR) has been proposed as an inflammatory biomarker and potential risk factor and prognosis predictor in cardiovascular disease (CVD).

Objective: To evaluate the association between the NLR and the severity of coronary artery disease (CAD).

Methods: An observational and retrospective study was carried out, including 56 patients aged ≥ 18 years (41 men and 15 women) who underwent diagnostic and/or therapeutic coronary angiography from 2014 to 2019 at Sagrada Esperança Clinic, Luanda, Angola. Demographic data, risk factors and comorbidities, biochemical tests and full blood count were collected from the patients' medical reports. The NLR was calculated as the ratio between the total neutrophil and lymphocyte counts from the patients' full blood count. For the statistical analysis purposes, the sample was divided into two groups according to the median of NLR (median: 2.02): patients with NLR ≤median and patients with NLR> median. The statistical significance was set at 5%.

Results: The group of patients with CAD was relatively older than the group without CAD, although without any significant difference (58.49 ± 8.76 vs. 54.74 ± 8.7, p = 0.137). Likewise, the age was similar between groups considering the level of NLR (57.89 ± 8.60 vs. 56.54 ± 9.12, p = 0.571). The risk of having CAD and it being obstructive was twice as high in the group with NLR above the median (NLR > 2.02) compared to the group with a lower NLR (OR: 2.25, CI: 0.722 - 1.012 and 2.17, CI: 0.717 - 6.550, respectively). However, in general, our data suggested that there was no association between the neutrophil-lymphocyte ratio and the presence of CAD, nor with its severity (X^2 = 1.991, p = 0.259 and X^2 = 0.760, p = 0.562, respectively).

Conclusion: The risk of CAD occurrence, as well as the occurrence of obstructive CAD was twice higher in the group with higher neutrophil-lymphocyte ratio.

Keywords: *Cardiovascular Diseases; Inflammation; Neutrophil-Lymphocyte Ratio; Biomarkers; Atherosclerosis; Coronary Artery Disease*

Introduction

Cardiovascular diseases (CVD) are among the leading causes of death worldwide [1,2]. Approximately 17.7 million people died from CVD in 2015, with one third due to coronary artery disease (CAD) and stroke [2].

In recent years, the medical literature has highlighted the value of systemic inflammation as an important element in the development, progression and prognosis of atherosclerosis [3-5]. Several inflammatory markers have been shown to be useful in clinical studies in risk stratification and prognosis in patients with peripheral arterial disease (PAD), as well as in those with disease in other vascular beds such as the brain and coronary [6,7].

Many inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been associated with cardiovascular events [7,8]. CRP is associated with coronary artery disease (CAD), ischemic stroke and mortality from vascular and non-vascular causes [7,9]. Among the inflammatory markers, the neutrophil-lymphocyte ratio (NLR), defined as the ratio of the absolute neutrophil to lymphocyte count, has gained place as an effective biomarker in the stratification and prognosis of atherosclerotic CVD [10]. The NLR is a simple, relatively inexpensive, more available than any other marker, and has been shown to be a good predictor of multiple cardiovascular (CV) outcomes [11,12] that reflect an imbalance in inflammatory cells and the role of activated neutrophils in atherogenesis [13,14].

The role of NLR seems to begin even before any target organ injury has occurred, as demonstrated in a cohort in which a higher NLR was significantly correlated with an increased risk of developing hypertension compared to participants with lower levels (OR: 1.23; 95% CI 1.06 - 1.43) [15].

A high NLR is associated with the severity of CAD, as was evident in a cohort of 3,005 patients undergoing angioplasty for many indications, in which those with NLR > 3 had more severe obstructive CAD (OR: 2.45, $p < 0.001$) and worse prognosis, with higher rates of CV events (OR: 1.55, $p = 0.01$) in 3 years of follow-up [16]. The NLR is also predictor of death in patients with both stable ischemic heart disease [17] and acute coronary syndrome (ACS) [18,19]. A high NLR on admission for ACS is associated with in-hospital mortality from all causes (OR: 2.04, $p = 0.013$) and in 6 months of follow-up (OR: 3.88, $p < 0.001$) [20]. In patients undergoing invasive treatment, a high pre-intervention NLR was an independent predictor of in-stent restenosis after percutaneous coronary intervention (OR: 1.85, $p < 0.001$) [21], saphenous vein graft failure for those undergoing myocardial revascularization surgery [22] and cardiovascular mortality [23].

Among the clinical exams collected in all patients there is the complete blood count where the NLR can be easily calculated. Accordingly, we postulate that there could be a significant association between NLR, reflecting the inflammatory state and the severity of CAD, a condition associated with the occurrence of cardiovascular events and mortality, making it a guidance to the clinician to choose, in asymptomatic population with multiple risk factors, those most likely to have future complications and which could benefit from the indication of invasive and non-invasive strategies.

Methods

Study sample

An observational and retrospective study that included all patients who underwent a diagnostic and/or therapeutic coronary angiography over a period of 5 years (2014 - 2019) was carried out at Sagrada Esperança Clinic in Luanda, Angola.

The study included patients aged 18 years or older, who underwent at least one coronary angiography during the study period and who had the coronary angiography report available in the medical record or in the hemodynamic Department. In addition, it was necessary to have a complete blood count on admission (preferably within 24 hours prior to the coronary angiographic examination).

We excluded patients that complete blood count and/or coronary angiography information were not available or incomplete, infection diagnosis in the two weeks preceding the coronary angiography or current infection requiring antibiotic use, patients with hematological disorders, patients under immunosuppressive drugs (steroids) and patients with cancer.

Procedures

Data collection was made from the medical records of all patients who met the study criteria. A specific questionnaire was elaborated, and anthropometric and clinical data were collected directly from the patients' medical records, such as age, sex, race, residence, education and presence or absence of previous diagnosis of hypertension (HTN), diabetes, dyslipidemia, smoking and alcohol beverages consumption, biochemical tests and blood count were collected. The neutrophil-lymphocyte ratio for each patient was calculated as the ratio of the absolute neutrophil and lymphocyte count.

Coronary angiography and severity of coronary atherosclerosis

Coronary angiography was performed using the Judkins technique through the femoral artery (Siemens AXIOM ARTIS dTC, Erlangen, Germany). By reviewing the report of each angiogram, the location and percentage of stenosis among all coronary lesions was established.

Significant CAD was defined as the presence of stenosis of at least 50% of the vessel diameter in any of the main arteries, according to the injury classification proposed by the American College of Cardiology/American Heart Association [24].

The Gensini scoring system was used to determine the severity of CAD [25]. This method defines the narrowing of the coronary arteries lumen as 1 for stenosis from 1% to 25%, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99%, and 32 for total occlusion. The score is then multiplied by a factor representing the importance of the injury location in the coronary artery system. For location scores, 5 points are given for left main coronary artery injury; 2.5 for the proximal third of the anterior descending (AD) or circumflex artery (CX); 1.5 for middle third of AD and CX; 1 for distal third of AD and CX, first diagonal, first branch of obtuse marginal, right coronary, posterior descending artery and intermediate artery; 0.5 for the second diagonal and branches of the second obtuse marginal.

Patients with stenosis were divided into two groups according to the Gensini score: with mild atherosclerosis (Gensini score 1 - 29) and severe atherosclerosis (Gensini score ≥ 30).

Statistical analysis

Data were analyzed with SPSS software (SPSS for Windows 21.0, SPSS, Inc., Chicago, IL). Data distribution was determined using the Kolmogorov–Smirnov test. Continuous variables are presented as mean and SD or as median and range if they are not normally distributed and were analyzed by the independent-samples t-test and Mann-Whitney U test, when suitable. Categorical data are presented as percentages and analyzed by Chi-square test. The association between variables was performed by the Chi-square test. The Odds Ratio was calculated to define the risk of occurrence of CAD as well as risk of obstructive CAD. For the purposes of statistical analysis, according to the median neutrophil-lymphocyte ratio, the patients were divided into two groups: (1) those with an NLR above the median and (2) patients with NLR equal to or less than the median. Statistical significance was set at 5%.

Results

The present study included a total of 56 patients who underwent coronary angiography, of which 37 (66.1%) had some degree of coronary artery disease as diagnosis and 19 (33.9%) had normal exams. Among all exams performed, 29 (51.8%) were elective and 27 (48.2%) with an emergency indication. The indications for the exams were respectively: Acute Myocardial Infarction (41.1%), unstable angina (21.4%) and stable angina (37.5%).

The general characteristics of the sample were assessed taking into account the level of inflammation with cut-off point of 2.02 for the neutrophil-lymphocyte ratio (Table 1). Statistically significant differences were registered in race and full whit count cells parameters.

Characteristic	NLR ≤ median, (n = 28)	NLR > median, (n = 28)	P value
Age, years, mean ± SD	57.89 ± 8.60	56.54 ± 9.12	0.571
Gender			
Male, n (%)	21 (75.00)	20 (71.40)	0.765
Female, n (%)	7 (25.00)	8 (28.60)	
Race			
Black, n (%)	22 (78.60)	14 (50.00)	0.043
Other, n (%)	6 (21.40)	14 (5.00)	
Nationality			
Angolan, n (%)	23 (82.10)	18 (64.30)	0.135
Other, n (%)	5 (17.90)	10 (35.70)	
SBP, mean ± SD	141.18 ± 17.51	143.14 ± 28.29	0.760
DBP, mean ± SD	83.79 ± 10.75	86.75 ± 18.58	0.469
HR, mean ± SD	72.18 ± 14.20	77.46 ± 16.03	0.197
Risk Factors			
CAD familial history, n (%)	2 (7.10)	3 (10.70)	0.976
Smoking, n (%)	8 (28.60)	13 (46.40)	0.171
Hypertension, n (%)	23 (82.10)	17 (60.70)	0.079
Diabetes Mellitus, n (%)	7 (25.00)	7 (25.00)	1.00
Dyslipidemia, n (%)	12 (42.90)	8 (28.60)	0.269
Hematological Parameters			
Hemoglobin, mean ± SD	13.4 ± 1.6	13.5 ± 2.0	0.818
Platelets, 103/µL, mean ± SD	230.5 ± 87.7	254.3 ± 98.1	0.342
WBC, 103/µL, mean ± SD	6.3 ± 2.2	9.6 ± 4.1	0.001
Neutrophils, 103/µL, mean ± SD	2.9 ± 1.2	6.9 ± 3.9	< 0.001
Lymphocytes, 103/µL, mean ± SD	2.3 ± 0.6	1.8 ± 0.4	< 0.001
NLR, mean ± SD	1.3 ± 0.5	4.0 ± 2.6	< 0.001
Creatinine, mg/dL, mean ± SD	1.0 ± 0.4	1.2 ± 0.8	0.363

Table 1: *General characteristics of sample according to the median of neutrophil-lymphocyte ratio.*

Note: CAD: Coronary Artery Disease; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; HTN: Hypertension; HR: Heart Rate; NLR: Neutrophil-Lymphocyte Ratio; SBP: Systolic Blood Pressure; SD: Standard Deviation; WBC: White Blood Cells. Median = 2.02.

Table 2 shows the occurrence and severity of coronary disease between the groups taking into account the level of the neutrophil-lymphocyte ratio above or below the median. There were no significant differences in both the occurrence and severity of coronary artery disease.

Characteristic	NLR ≤ median, (n = 28)	NLR > median, (n = 28)	P Value
Cardiac Catheterism			
Without lesions	12 (42.9)	7 (25.0)	0.162
With lesions	16 (57.1)	21 (75.0)	
Presence of obstructive CAD			
Yes	15 (53.6)	20 (71.4)	0.171
No	13 (46.4)	8 (28.6)	
CAD Severity			
No CAD	12 (42.9)	8 (28.6)	
One vessel	6 (21.4)	10 (35.7)	0.483
Two vessels	7 (25.0)	6 (21.4)	
Three vessels	3 (10.7)	4 (14.3)	
Gensini Score			
1 - 29	21 (75.0)	18 (64.3)	0.388
≥ 30	7 (25.0)	10 (35.7)	

Table 2: *Presence and CAD severity according to the NLR sample median (2.02).*

Note: CAD: Coronary Artery Disease; NLR: Neutrophil-Lymphocyte Ratio.

The association between the level of inflammation and the occurrence of coronary artery disease is shown in table 3. There was no association between the neutrophil-lymphocyte ratio and coronary artery disease diagnosis. Likewise, there was no association between the neutrophil-lymphocyte ratio and the severity of coronary artery disease (Table 4). However, the risk of having the diagnosis of coronary artery disease, as well as the presence of obstructive CAD, was twice as high in the group with the higher NLR compared to the group with lowest NLR (OR: 2,250 and 2,167 respectively). The group with NLR greater than the median still had 39% higher risk of having greater extension of CAD assessed by Gensini score (Table 5).

Group	Coronary Angiogram		P value	Total, n (%)
	Without CAD, n (%)	With CAD, n (%)		
NLR ≤ median	12 (42.9)	16 (57.1)	0.259	28 (100.0)
NLR > median	7 (25.0)	21 (75.0)		28 (100.0)
Chi-square Test (X^2) = 1.991				

Table 3: *Association between inflammation and coronary artery disease presence coronary angiogram.*

Note: CAD: Coronary Artery Disease; NLR: Neutrophil-Lymphocyte Ratio.

Group	Coronary Angiogram		P value	Total, n (%)
	Gensini score ≥30, n (%)	Gensini score 1-29, n (%)		
NLR> median	10 (35.7)	18 (64.3)	0.562	28 (100.0)
RNL≤ median	7 (25.0)	21 (75.0)		28 (100.0)
Chi-square Test (X^2) = 0.760				

Table 4: *Association between inflammation level and obstructive coronary artery disease.*

Designation	Odds Ratio	Confidence Interval 95%
Risk of occurrence of CAD	2.250	0.722 - 1.012
Risk of obstructive CAD	2.167	0.717 - 6.550
Risk of greater extension of CAD	1.389	0.450 - 4.286

Table 5: *Risk of occurrence of CAD and degree of obstruction according to the NLR above the median.*

Arterial hypertension was the most frequent risk factor (71.4%), followed by smoking (37.5%), dyslipidemia (35.7%), diabetes (25%) and family history of CAD (8.9%), respectively. The most prescribed drugs for patients were Aspirin (84.4%), Statins (66.1%), beta-blockers (66.1%), angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) 25%, respectively. The prescription of drugs as part of the treatment of CAD in order of frequency was, respectively: Aspirin (80.4%), Statins (66.1%), Beta-blockers (53.6%), ACEI (39.3%) and ARB (25%).

Discussion

The main finding of the present study was that the risk of coronary artery disease as well as the occurrence of obstructive CAD was twice as high in the group with the higher NLR compared to the group with the lower NLR. However, data from the present study did not indicate any association between the neutrophil-lymphocyte ratio, the presence of coronary artery disease, or its severity.

Although current evidence indicate the existence of association between NLR and coronary artery disease [16], our data did not confirm this finding. The lack of association registered in our study might be due to the sample size, which did not have enough statistical power to demonstrate significant differences between the groups and the retrospective nature of the study itself. However, it is noteworthy that despite this, our data indicated that patients with NLR above the median, defined in the present study as value above 2.02, had higher risk of occurrence of CAD and obstructive CAD, with an odds ratio of 2.25 and 2.17 respectively.

The NLR was introduced as a potential marker for determining inflammation in heart and non-heart disease. Although, still with no universally defined cutoff point, higher values of NLR have been constantly related to a higher frequency of CAD and worse progression of patients admitted for ACS. Our data show that the group of patients with NLR above the median (> 2.02) had a risk of occurring CAD and was twice more obstructive than the group with NLR lower than the median.

In a cohort study of three groups according to the NLR value stratified into three groups (< 2, 2 - 3, and > 3), NLR was independently associated with the severity of CAD and contributed significantly to the regression models [16]. Patients with NLR > 3 had more advanced obstructive CAD (OR = 2.45, 95% CI 1.76 - 3.42, $p < 0.001$) and worse prognosis, with a higher rate of major CV events during the 3-year follow-up (OR = 1.55, 95% CI 1.09 - 2.2, $p = 0.01$). In addition, meta-analysis studies indicate that NLR is a marker of all-cause mortality and cardiovascular events [26]. Several other authors found that NLR was associated with the severity of coronary artery disease [27].

The NLR is considered one of the strongest leukocyte predictors of adverse outcomes for stable CAD, long-term mortality in acute myocardial infarction (AMI) with ST-segment elevation, and in-hospital mortality in acute coronary syndromes [11]. Several other studies point out that NLR is a marker of mortality in patients with ischemic heart disease for both stable CAD [17] and ACS [16,18]. A high NLR at the admission of patients with ACS was associated with higher in-hospital mortality from all causes (OR: 2.04, $p = 0.013$) and at 6 months (OR: 3.88, $p < 0.001$) [20]. In patients treated with angioplasty, a high pre-intervention NLR was an independent predictor of in-stent restenosis (OR: 1.85, $p < 0.001$) [21], the greatest failure of the saphenous vein graft for those undergoing myocardial revascularization surgery [22], and cardiovascular mortality [23]. In addition, in analyzes of cohort studies with patients undergoing coronary artery bypass grafting or coronary angiography, a high NLR increased the risk of cardiovascular and all-cause mortality by two [24].

Arterial hypertension was the most prevalent risk factor and aspirin (80.4%), beta-blockers (53.6%) and ACE inhibitors (39.3%) were the most prescribed drug classes. The association of hypertension and coronary artery disease is a frequent finding. There are many pathophysiological mechanisms that link the two diseases. Hypertension induces endothelial dysfunction, exacerbates the atherosclerotic process and contributes to making the atherosclerotic plaque more unstable [28]. Recommendations for prescribing drugs in these patients include those, not only with antihypertensive properties, but also cardioprotective. Classes include beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins and aspirin [29].

Limitations of the Study

The present study is not exempt from the limitations inherent to retrospective studies, and there may be bias both in data collection and in its analysis. The absence of an association between the NLR and the registered CAD may be due to the sample size, which may have caused the absence of sufficient statistical power to detect the differences between the groups. Prospective studies with better designs and greater static power are necessary to better assess the characteristics of the patients that represent our population and to better establish the association between the neutrophil-lymphocyte ratio and coronary disease in our population.

Conclusion

The data from the present study did not show any association between the neutrophil-lymphocyte ratio and coronary artery disease in the sample of the study. However, the group with higher NLR had two fold much higher risk of having coronary artery disease and much more obstructive coronary artery disease.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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Author Contributions

Muela HCS: Designed and performed research, analyzed data, and wrote the manuscript; Franco GML, Sandala FM, Tito JAJ, dos Santos JRV, Francisco AGB: Performed research; Lopes ICA, Silva ABT; Magalhães P: Reviewed and contributed for the manuscript.

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