

Correlation between neutrophil to lymphocyte ratio and coronary calcium score in CT angiography. NLR and coronary calcification

Correlación entre la relación de neutrófilos a linfocitos y la puntuación de calcio coronario en la angiografía por TC. La RNL y calcificación coronaria

Hamidreza Varastehrahan¹, Aryan Naghedi¹ , Arvin Naghedi², Seid Kazem Razavi-Ratki³ , Nasim Namiranian⁴ , Reza Nafisi Moghadam³ , Ali Pedarzadeh¹ 

1. Department of Cardiology, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

2. Department of Mathematics, Yazd University, Yazd, Iran

3. Department of Radiology, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

4. Department of public health and epidemiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Correspondencia

Aryan Naghedi

Department of Cardiology, Shahid Sadoughi Hospital,
Shahid Sadoughi University of Medical Sciences, Yazd, Iran
E-mail: a.naghedi@yahoo.com
Tel.: +989381561737

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Abstract

Background: cardiovascular diseases are the most common causes of death worldwide. Atherosclerosis is the most important etiology for cardiovascular diseases. Nowadays, atherosclerosis is defined as a chronic inflammatory disease. Among the most important inflammatory markers, WBC is said to be a risk factor for cardiovascular events and mortality. Among different WBC subtypes, neutrophil and thus neutrophil to lymphocyte ratio (NLR) is an important predictor for mortality and morbidity. Based on this, in this study we aimed to investigate the correlation between NLR and coronary artery calcification.

Patients and methods: This research is a cross-sectional study of correlation type. A total of 353 consecutive patients were enrolled with stable angina referred to Afshar heart center for elective CT-angiography. Patients were divided into 4 groups based on NLR and the patients' data was analyzed using SPPSS ver.26 software.

Results: In this study a total of 353 patients were investigated which included 159 women and 194 men. The patients ages ranged between 19 and 80 and the average age was 53 years. We found a statistically significant difference in coronary calcium score (CCS) between patients in fourth quartile of NLR and other patients (P-Value<0.001). Spearman's correlation test with $r=0.420$ and P-Value<0.001 indicated a positive correlation between NLR and CCS.

Conclusion: Based on the results of present research its concluded that NLR is correlated with CCS and patients with NLR above 2.42 are in danger of higher risk of coronary artery calcification.

Keywords: Computed tomography angiography, neutrophil to lymphocyte ratio, inflammation, coronary artery disease.

Resumen

Antecedentes: las enfermedades cardiovasculares son las causas más comunes de muerte en todo el mundo. La aterosclerosis es la etiología más importante para las enfermedades cardiovasculares. Hoy en día, la aterosclerosis se define como una enfermedad inflamatoria crónica. Entre los marcadores inflamatorios más importantes, se dice que el conteo sanguíneo completo (CSC) es un factor de riesgo para eventos cardiovasculares y mortalidad. En base a esto, en este estudio nuestro objetivo fue investigar la correlación entre la relación de neutrófilos a linfocitos (RNL) y la calcificación de la arteria coronaria.

Pacientes y métodos: esta investigación es un estudio transversal correlacional. Un total de 353 pacientes consecutivos se inscribieron con angina estable remitidos al centro cardíaco Afshar para una angiografía por TC electiva. Los pacientes se dividieron en 4 grupos según RNL y los datos de los pacientes se analizaron utilizando el software SPPSS ver.26.

Resultados: En este estudio se investigó un total de 353 pacientes que incluyeron 159 mujeres y 194 hombres. La edad promedio fue de 53 años. Encontramos una diferencia estadísticamente significativa en la puntuación de calcio coronario (PCC) entre pacientes en el cuarto cuartil de RNL y otros pacientes (valor $P<0,001$). La prueba de correlación de Spearman con $r=0,420$ y valor $P<0,001$ indicó una correlación positiva entre RNL y PCC.

Conclusión: Con base en los resultados de la presente investigación, se concluyó que la RNL se correlaciona con PCC y los pacientes con RNL por encima de 2,42 tienen un mayor riesgo de calcificación de la arteria coronaria.

Palabras clave: Angiografía por tomografía computarizada, relación de neutrófilos a linfocitos, inflamación, enfermedad de la arteria coronaria.

Introduction

Cardiovascular diseases are the most important and the most common causes of death worldwide and are developing rapidly in both developed and developing countries. They cause 38% of death in USA and are the most common causes of death in European men below 65¹⁻⁴.

Nowadays atherosclerosis is known to be the most important etiology for cardiovascular diseases and is responsible for a high number of mortality around the world⁵. Atherosclerotic lesions are asymmetric focal thickening of the intima and include cells, connective tissue, fat and debris¹.

In recent literature, atherosclerosis is considered to be a multifactorial inflammatory disease which is affected by both intrinsic and extrinsic factors and plays a very important role in all stages of cardiovascular diseases^{6, 7}.

It is reported that during atherosclerosis, monocytes and macrophages and other inflammatory cells penetrate the atherosclerotic plaque and initiate an inflammatory process by releasing inflammatory mediators^{1, 5}. In different up to date studies the role of systemic inflammation besides local inflammation is described and the effects of different inflammatory factors such as erythrocyte sedimentation rate(ESR), C-Reactive Protein(CRP), different interleukins and platelet in atherosclerosis is investigated⁸⁻¹¹.

Among the most important inflammatory factors which are recently investigated, white blood cell(WBC) can be mentioned. WBC is considered to be as a predictor for cardiovascular events and mortality risk solely¹²⁻¹⁵. Different manuscripts have concluded that WBC can make it is possible to detect high risk patients that are not yet detected using traditional methods¹⁶⁻¹⁹.

Among different WBC subtypes, it is seen that neutrophil and thus neutrophil to lymphocyte ratio(NLR) is an important predictor for mortality and morbidity in patients with myocardial infarction and stable angina pectoris. Elevated neutrophil count in considered to be a principal factor for severity of coronary artery involvement in different articles. The severity of coronary artery disease was assessed using different methods in these articles^{20, 21}.

Neutrophilia can lead to a hypercoagulability state and increased blood viscosity. Neutrophilia may also cause microvascular injury in interaction with platelets and endothelium. Neutrophils also play a key role in reperfusion injury²².

In this study we aimed to achieve precise estimation about the relationship between NLR and coronary artery calcification observed in computed tomography(CT) angiographic imaging and investigate the correlation

between coronary calcification score (CCS) in CT-angiography and NLR.

Patients and methods

Present study is a correlation type cross-sectional study performed on 353 consecutive patients with stable angina pectoris referred to Afshar heart center for elective CT-angiography during 2019.

We included all symptomatic patients aged between 18 and 80 with susceptible coronary artery disease admitted for CT angiography that carry a complete blood count(CBC) diff test within 1 month of imaging. All patients older than 80 years, WBC more than 10000 cells/ μ L and a history of vascular events such as myocardial infarction or cerebrovascular events were excluded. We also excluded all patients with active infection, fever or known cases of diseases that may be associated with leukocytosis or increased polymorph nuclear (PMN) ratio.

This study was registered in committee of ethics in medical research of Shahid Sadoughi university of medical sciences and health care services, Yazd, Iran with IR.SSU.MEDICINE.REC.1398.004 approval code. All patient signed a written informed consent and the study was designed and performed based on declaration of Helsinki.

In all patients the blood sample was collected from antecubital vein after 12 hours of fasting. The analysis of CBC was done using Sysmex XT-2000i (Sysmex, Kobe, Japan). The CBC test was not performed longer than 1 month before or after coronary CT-angiography.

All CT-scans were conducted via a 64 slice multi-detector CT scan device (Toshiba Medical Systems, Japan) with a heart rate <65 beats/minute. Patients coronary calcium score was reported by two expert cardiologists in LAD (left anterior descending), LM (left main), RCA (right coronary artery) and CX(circumflex) arteries and a total coronary calcium score was also calculated.

Neutrophil to lymphocyte ratio was simply calculated by dividing absolute neutrophil count to absolute lymphocyte count. Patients were divided into 4 groups based on NLR quartiles: Q1 \leq 1.37, Q2= 1.37-1.75, Q3= 1.75-2.42 and Q4 \geq 2.42.

All recorded data including calcium score of each artery, number of lesions in each artery, total calcium score, patients ages, gender and CBC diff were entered into SPSS Ver.26 software for further statistical analysis.

Considering highly skewed data and lack of normal distribution in both CCS and NLR, non-parametric kruskal-Wallis H test was used to investigate the differences of

CCS between groups of patients based on NLR quartiles and Dunn-Bonferroni posthoc test was used for pairwise comparison. To assess the correlation between NLR and CCS, Spearman's correlation test was used. For all tests a 2-tailed P-value<0.05 was considered to be statistically significant.

Results are reported in a table as frequency, percentage and mean±SD. Bar chart, scatter plot and posthoc pairwise comparison matrix are used for data visualization.

Results

Present study was performed on patients with stable angina referred to Afshar heart center for elective CT-angiography. All included patients had a CBC diff test performed within 1 month of imaging.

In this study we enrolled 353 consecutive patients which included 159 (45%) women and 194 (55%) men. The patients aged between 19 and 80 and the average age of patients was 53.44±12.14. Mean NLR was 2.41±2.04 in this study sample.

In this study we observed that LAD artery has the most number of lesions and LM artery contains minimum number of lesions. Highest CCS was recorded to be in LAD artery and RCA was recorded to have lowest calcification score. The total CCS recorded in our study ranged between 0 and 2606 (96.81±282.62). In **table I**, number of lesions and associated calcium score (Mean±SD) with each vessel is reported.

Table I: Descriptive statistics related to calcification status of each vessel.

Vessel	Variable	Number of lesions	Calcium score
LM		18 (6%)	116.46±236.02
LAD		128 (45%)	143.13±197.33
CX		78 (28%)	116.1±237.75
RCA		59 (21%)	78.85±133.39
Total		283 (100%)	96.81±282.62

Quantitative CCS was investigated if is significantly different among 4 groups using non-parametric Kruskal-Wallis test. Kruskal-Wallis test provided very strong evidence of a difference (H=79.608, P-value<0.001) between mean ranks of at least one group. The bar chart in **figure 1** shows mean CCS in each quartile of NLR.

As seen in **figure 2**, Dunn-Bonferroni pairwise comparison tests revealed that there is a statistically significant difference in CCS in patients in 4th quartile of NLR compared to other patients in other quartiles. There was no evidence of difference between other pair of groups.

Rather than this we also used Spearman's correlation test to check the relationship between NLR and CCS and the results showed a statistically significant positive

correlation between NLR and CCS with P Value<0.001 and r=0.42. The associated scatter plot is under the name of **figure 3** below:

Figure 1: Bar chart demonstrating mean CCS in different quartiles of NLR. Mean total CCS is 267.74, 54.44, 46.11 and 19.75 in Q4, Q3, Q2 and Q1 quartiles respectively.

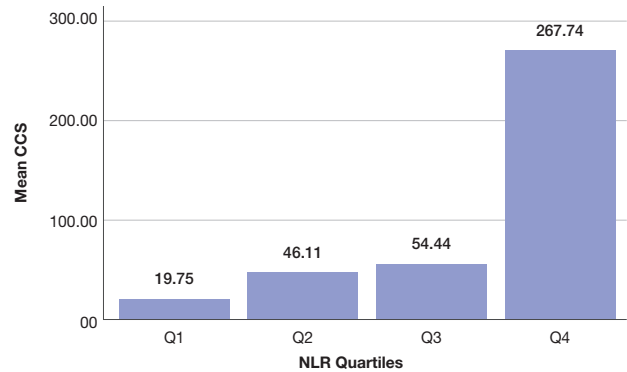


Figure 2: Each node shows the average rank. There is a statistically significant difference between Q1-Q4 (P-value<0.001), Q2-Q4 (P-value<0.001) and Q3-Q4 (P-value<0.001) but there is no significant difference between Q1-Q2, Q2-Q3 and Q1-Q3 pairs.

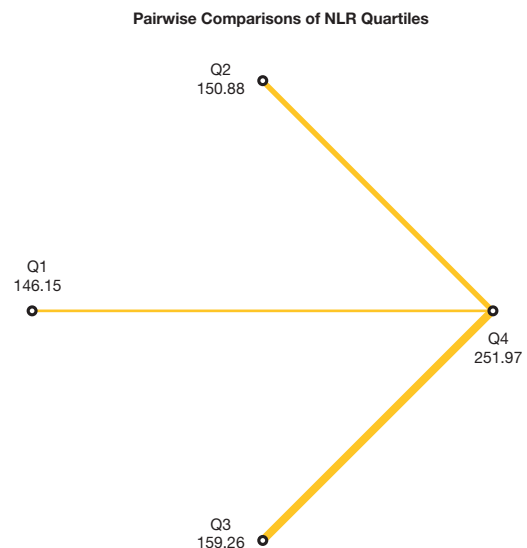
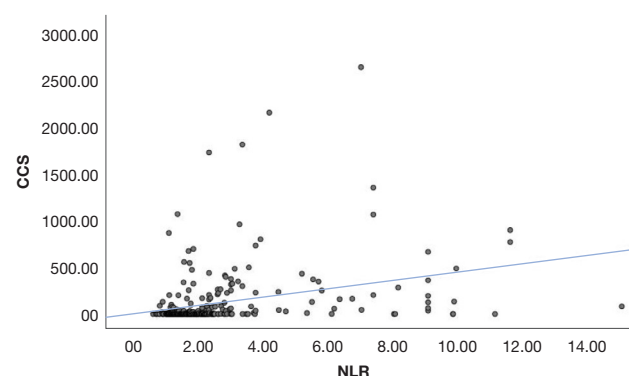


Figure 3: Scatter Plot, coronary calcium score (CCS) as dependent variable and neutrophil to lymphocyte ratio (NLR) as independent variable. There is a positive linear correlation between two variables.



Discussion

Cardiovascular diseases are the most common cause of death around the world and are spreading in both developed and developing countries. This means that the prevention and prediction of cardiovascular diseases need serious revisions¹⁻⁴.

Among cardiovascular diseases, coronary artery diseases and specially atherosclerosis are the most common cause of mortality around the world(5). Other risk factors of coronary artery diseases based on Framingham study consist of age, sex, hypertension(HTN), diabetes mellitus(DM), dyslipidemia and smoking²³.

Based on modern studies, atherosclerosis is defined to be multifactorial and chronic low grade inflammatory process and involves other cardiovascular risk factors such as DM, HTN, metabolic syndrome, obesity, dyslipidemia and endothelial dysfunction and is not only a passive injury caused by lipid deposition on vascular wall^{7, 23}. During atherosclerosis process, macrophages, monocytes and inflammatory cells penetrate the atheroma and cause inflammatory process to initiate^{1, 5}.

Among different modern inflammatory markers, homocysteine, high sensitivity CRP, interleukin 6 (IL-6), phospholipase A2, leukocytes, neutrophils, lymphocytes and NLR are reported to be related to atherosclerosis progression and initiation, destabilization and rupture of plaque and thrombotic events and severity of coronary artery disease(CAD)^{21, 24}. There is a positive correlation between NLR and commonly used inflammatory markers but unlike other inflammatory markers, NLR is inexpensive and easily available¹².

In this study we focused on NLR as an inflammatory marker which is reported to be better, more accurate and more stable than WBC count in prediction of clinical outcomes in acute decompensated heart failure and results after percutaneous coronary intervention(PCI), and coronary artery bypass graft(CABG), specially, in patients with acute presentations^{21, 24, 25}. A higher NLR, even with a normal WBC count is related with higher risk for atherosclerotic events and progression of atherosclerosis¹².

In animal models it is seen that there is a neutrophil invasion in atherosclerotic plaques and neutrophils make the atherosclerotic plaque more vulnerable by releasing more proteolytic enzymes, arachidonic acid derivative and superoxide radicals. Interaction between neutrophil and endothelium also seems to be a reason for endothelial damage and thus atherosclerosis¹². It is also proved that stimulated WBCs have a higher tendency to adhere to vascular endothelium and they penetrate intima and cause capillary leukostasis. Higher levels of NLR have also been reported to be associated with a higher sympatic/parasympatic activity²⁶.

Recently coronary calcium score is believed to be a sensitive marker of coronary artery atherosclerosis and is named among modern modalities to estimate severity of CAD and coronary artery calcification and stiffness⁸.

In this study we investigated the relationship between severity of coronary calcification detected in CT angiography and NLR as a modern inflammatory marker.

Our results showed a significant relationship between NLR and CCS in patients with stable angina pectoris.

We divided our study population (353 symptomatic patients with stable coronary artery disease) into 4 groups based on NLR quartiles and a strong correlation was observed between NLR and CCS in patients in 4th quartile of NLR compared to other quartiles.

In different studies, it is reported that patients with acute coronary syndrome, stable and unstable angina in higher tertile of NLR are at higher risk of in hospital, 6month, 3 years and 4 years mortality^{13, 17, 20}. In a study performed in America in 2008 it was concluded that NLR shows significant temporal variations and it seems that NLR is a dynamic variable²⁰.

In a Turkish study in 2013 which was performed on patients with ST segment elevation myocardial infarction(STEMI), it was reported that NLR rises in first 96 hours of symptoms onset and is correlated with increased mortality rate²¹.

Papa et al worked on predictive ability of NLR in Italy and they discovered that event free survival in documented stable CAD according to NLR tertiles is: 99% for 1st tertile, 96.5% for 2nd tertile and 88.8% for 3rd tertile⁶.

In this study we used CCS to assess severity and complexity of coronary artery disease. There were other studies that used angiography technique and used Gensini and SYNTAX score to assess the severity of coronary artery disease and they concluded the same results as us. They worked on STEMI, stable angina and unstable angina patients and reported that NLR, ejection fraction(EF), DM, hyperlipidemia(HLP), glomerular filtration rate(GFR), creatinine, Neutrophil count and age are independent predictor of SYNTAX score^{7, 21, 27}. In a study performed in china in 2014, researchers showed that NLR indicates presence of CAD and with a cutoff of 2.04 is good for predicting high Gensini score (GS) (GS>41)¹⁶.

The physiopathology of atherosclerosis and aortic valve sclerosis (AVS) and mitral annular calcification (MAC) is similar to coronary artery disease, atherosclerosis, heart failure and stroke and the role of systemic inflammation is well explained in all of them. NLR along with red cell distribution width(RDW), intracellular adhesion molecule 1 and IL-6 was also higher in patients diagnosed with MAC and AVS^{26, 28, 29}.

In a study performed in Sweden in 2014, researchers found that NLR can indicate severity of CAD and cardiovascular prognosis. They concluded that in patients with non ST segment elevated acute coronary syndrome (NSTEMI ACS) and stable angina(SA), NLR is correlated with non-calcified plaques. They said that NLR reflects the burden of vulnerable plaques in CAD³⁰.

NLR is an independent prognostic marker of severe atherosclerosis together with glucose, age and high density lipoprotein(HDL). In a study that enrolled only patients with type two diabetes mellitus(T2DM) it was also observed that risk of obstructive CAD and CCS as a marker for ischemic CAD is higher in patients with higher NLR³¹.

In a valid study published in valuable journal of American college of cardiology, the researchers investigated correlation between CCS and luminal obstruction detected in angiography and they concluded that CCS can detect atherosclerotic plaques with a sensitivity of 88% and CT angiography has a 97% of sensitivity in detecting angiographic stenosis of more than 70%. In this study researchers reported that a same stenosis in angiography, can be detected in men 1.81 fold more than in women. They hypothesized that this difference can be due to different pattern of calcification in two genders³².

In a study performed by Turkish researchers in 2014 it was observed that NLR is not correlated with plaque morphology but they detected that coronary artery atherosclerosis detected by 64 slice computed tomography imaging is higher in patients in 3rd tertile of NLR compared to other patients³³.

In a study performed in 2015, it was reported that Inflammatory conditions lead to increased activity of megakaryocytes too. They also reported that low lymphocyte count is related with worse cardiovascular outcomes in patients

with CAD and chronic heart failure. Lymphocytes represent a better immune response while neutrophils cause a destructive immune reaction. Turkish researchers concluded that platelet to lymphocyte ratio(PLR) can be used as a new prognostic marker for cardiovascular events, cancer patients and critical limb ischemia. They also stated that PLR is a predictor of severe atherosclerosis and is positively correlated with GS³⁴.

In a review article they concluded that based on present studies, NLR can be soon used as a marker for cardiovascular diseases because of cheap price and high accessibility. NLR is officially included in the list of inflammatory markers and is related with CCS, arterial stiffness, arrhythmias during PCI, in-stent restenosis, and prognostic marker for outcomes of CABG and post CABG atrial fibrillation(AF)^{14, 21, 35}. NLR is a good biomarker to find patients that need a more aggressive treatment and a closer follow-up³⁴.

Conclusion

Our study had a high study population in its kind and in this study we concluded that NLR with a cutoff of 2.42 is strongly correlated with CCS with a P-value<0.001.

Conflict of interests

The authors declare no conflict of interests.

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