

## REVIEW ARTICLE

## Neutrophil-Lymphocyte Ratio in Cardiovascular Disease Risk Assessment

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### Abstract

The development of cardiovascular diseases with atherosclerotic origin is associated with a severe inflammatory process. Neutrophils and lymphocytes are cells sensitive to this type of disorder and their ratio, known as the NLR (neutrophil/lymphocyte ratio), has shown to be useful in clinical practice. The aim of this study was to assess the role of NLR in cardiovascular disease risk assessment. We carried out a literature review in the PubMed databases searching for articles published between 2001 to 2017 and found that NLR is in fact a useful marker for cardiovascular disease. Using NLR in patients at cardiovascular risk would be useful to delineate the prognosis of patients with this disease pattern.

### Introduction

Among the diseases that affect humans, those related to the cardiovascular system warrant great prominence.<sup>1,2</sup> Currently, these diseases account for more than 17 million deaths worldwide each year, and the estimate for 2030 is that this figure will reach 23.6 million, with acute myocardial infarction being the most common cause of these deaths.<sup>3,4</sup>

Very often, this cardiac event is associated with the appearance of atheroma plaques lodged in the intima layers of the coronary arteries, triggering inflammatory processes. This risk factor may be diagnosed by the concentration/amount of inflammatory markers found in the peripheral blood, such as neutrophils and lymphocytes.<sup>4,5</sup>

### Keywords

Cardiovascular Diseases / physiopathology; Biomarkers; Neutrophils; Leukocyte Count; Atherosclerosis / physiopathology; Inflammation.

Considering the potential of these different cell types, i.e., neutrophils and lymphocytes, in the genesis and evolution of atheroma plaques, the neutrophil/lymphocyte ratio (NLR) has a high diagnostic potential for cardiovascular diseases. Neutrophil and lymphocyte analyses are simple, relatively inexpensive, and widely available.<sup>6</sup> Therefore, this review aimed to discuss the importance of NLR and its inclusion in the list of useful tools for the diagnosis/prognosis of atheroma-related heart disease.

### Atherogenesis and the Neutrophil/Lymphocyte Ratio

As shown in figure 1, endothelial dysfunctions related to atherosclerotic plaques are usually associated with states of neutrophilia, together with lymphopenia processes. The antagonism between inducing and protective factors of inflammatory processes favors the onset of injuries in the vascular endothelium, as well as the onset of atherosclerosis.

The body is exposed to systemic stress in the immunological lack of control due to the inflammatory process related to cardiovascular diseases, increasing the levels of cortisol and catecholamines, so that the lymphocytes are affected by this imbalance, weakening its role in modulating the inflammatory response.<sup>7-9</sup>

Infarcted patients have elevated cortisol levels. This increase induces the reduction of lymphocytes by apoptosis, and CD4+ and CD8 cells become more sensitive to tumor necrosis factor-alpha (TNF- $\alpha$ ).<sup>10</sup> This is one of the most likely mechanisms to explain lymphopenia developed during cardiovascular disease evolution. However, the pathophysiological mechanism of this decrease has not yet been fully elucidated.<sup>9</sup>

On the other hand, mechanisms related to neutrophilia in cardiovascular diseases are more clarified,

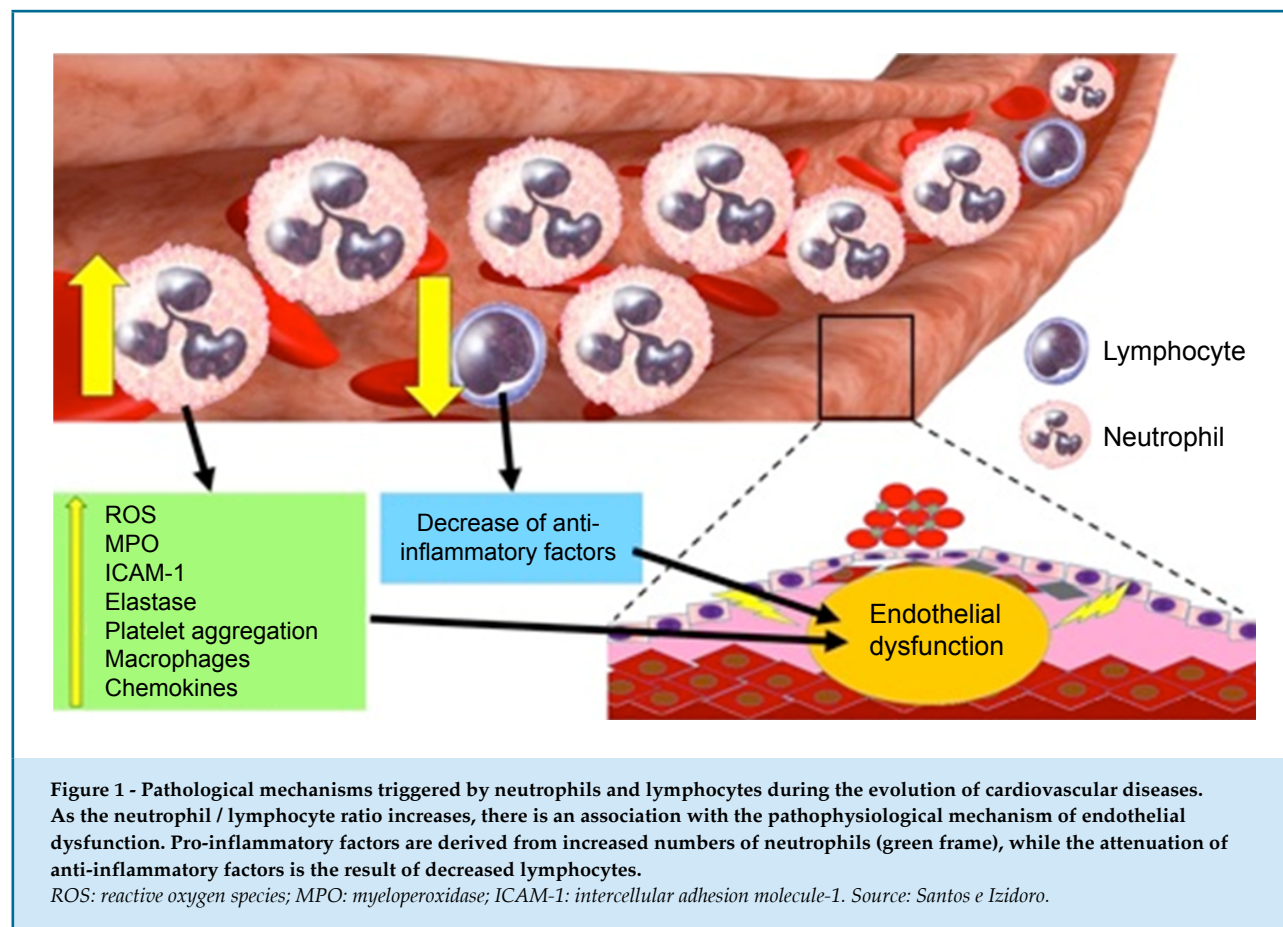
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especially in atherosclerosis. Neutrophils are related, since the initial phase, to a more advanced stage of atherosclerosis, participating in the inflammatory process as a hyperlipidemia mediator, until the development of atherothrombosis, infiltrating the atherosclerotic arteries.<sup>11</sup>

In such pathophysiological circumstances, it seems that the increase in neutrophils is associated with the maturation stage of these cells, exhibiting nuclear segmentation.<sup>10,12-15</sup> Therefore, it is more likely that the predominant neutrophilia originates from the segmented cell type, since atherosclerosis is a chronic inflammatory condition,<sup>16,17</sup> as well as the process of thrombosis.<sup>18,19</sup>

The neutrophils activate the macrophages, acquiring the lipid mediation function. Subsequently, macrophages express atherogenic factors, such as interleukin-6 (IL-6), CD40 and CD80, in addition to being susceptible to foam cell formation.<sup>7,8,20-25</sup> The neutrophil cells, themselves, also express atherogenic factors, such as chemokines and cytokines.<sup>11</sup>

When myocardial tissue damage occurs, leading to inflammation, neutrophils are highlighted, releasing

arachidonic acid metabolites, chemokines, reactive oxygen species (ROS), intercellular adhesion molecules-1 (ICAM-1), platelet factors and several enzymes, such as myeloperoxidase (MPO) and elastase, facilitating the rupture of the atherosclerotic plaque by weakening the fibrotic layer, and the matrix ends up being degraded.<sup>3,11,26</sup>

MPO, an enzyme abundantly expressed in primary neutrophil granulocytes, is one of the most impacting components of endothelial dysfunction, as it limits nitric oxide and, through its catalytic activity, promotes the formation of oxidized low-density lipoprotein (LDL). Thus, subsequently, macrophages phagocytose the oxidized LDL, forming the foam cells.<sup>11</sup>

#### Pathological mechanisms originating from neutrophils and lymphocytes during cardiovascular diseases

Epidemiological evidence has shown the predictive role of NLR in atherosclerotic manifestations.<sup>27-30</sup> The states of lymphopenia disclosed by the whole blood count are associated with atherosclerosis progression, and the decrease in lymphocytes may be caused by apoptotic

processes triggered during atherosclerotic lesions.<sup>27</sup> On the other hand, the quantitative increase in neutrophils is also related to the atherogenic process, acting through lipid mediation, necrosis and inflammation, secreting chemokines and cytokines. This cell type regulates ICAM-1 and expresses MPO, a protein that contributes to the formation of free radicals, promoting greater LDL oxidation, exacerbating the pathological process.<sup>11</sup> Based on the interpretation of the NLR results, it is possible to predict the presence of atherosclerotic processes before the coronary angiography is performed.<sup>28,31</sup>

Additionally, this tool is useful to help attain a diagnosis of acute myocardial infarction more quickly and can be used in emergency situations in medical care units.<sup>32</sup>

The NLR is commonly increased in patients with coronary disease when compared to healthy patients. Neutrophil values and NLR are also correlated with the number of noncalcified atherosclerotic plaques, as shown by coronary assessment through angiotomography and invasive angiography.<sup>30</sup> Patients with total coronary occlusion also have a higher NLR value, being significantly more pronounced than in patients with normal coronary arteries ( $p < 0.001$ ).<sup>33</sup>

In a study of 194 volunteers with coronary artery disease submitted to coronary angiography,<sup>19</sup> those with severe atherosclerosis had higher neutrophil and lower lymphocyte percentages when compared to patients with mild atherosclerosis and normal individuals, and the NLR was higher than 2.5 in these conditions.

Recently, computed tomography coronary angiography studies have shown that increased NLR is associated with the presence, severity, and extent of atherosclerotic plaques in coronary arteries. A higher white cell and neutrophil counts and a lower absolute lymphocyte count were observed in the patients. A value of NLR higher than 2.25 increased the likelihood of developing coronary atherosclerosis (OR = 2.30) and critical luminal stenosis (OR = 2.60).<sup>17</sup>

The detection of obstructive coronary disease and coronary calcium score was significantly higher in type 2 diabetic patients with NLR higher than 2.05, when compared to patients with type 2 diabetes and NLR lower than or equal to 2.05.<sup>34</sup> In a retrospective study, it was observed that of 2,121 patients diagnosed with peripheral obstructive arterial disease and with NLR higher than 3.95, 680 of them had a higher percentile of acute myocardial infarction (48.5%) increase, previous

myocardial infarction (7%) and cerebrovascular accident (10%), when compared to patients with NLR < 3.95. Thus, the NLR higher than 3.95 was associated with an OR of 2.5 for acute myocardial infarction and showed higher levels of C-reactive protein (mean 5.6 mg/L) and high plasma fibrinogen levels (mean 412 mg/dL).<sup>35</sup>

### Neutrophil-lymphocyte ratio in cardiovascular diseases

In a meta-analysis involving ten cohorts, a higher relative risk (RR) of all-cause mortality was observed, due to the elevation of the NLR levels when compared with low levels (RR = 2.33), as well as of cardiovascular events in patients submitted to angiography or cardiac vascularization (RR = 1.89).<sup>3</sup> In an observational cohort containing 2,833 patients hospitalized with acute coronary syndromes, it was detected that NLR elevations are associated with higher chances of in-hospital mortality (OR = 2.04).<sup>26</sup>

In decompensated heart failure, of 1,212 individuals, patients with a higher tertile of NLR, showing a mean of 9.6, had an increase in the mortality rate during an average follow-up of 26 months. Nevertheless, the highest tertile of NLR was associated with older age, systemic arterial hypertension, diabetes mellitus, history of coronary artery disease and arterial fibrillation. In the blood sample analyses, the highest NLR tertile was associated with the increase in B-type natriuretic peptide, urea, serum creatinine and hemoglobin levels. Consequently, the chest x-ray examination showed that the highest tertile of the NLR was associated with a higher incidence of cardiomegaly, pleural effusion and interstitial edema.<sup>36</sup>

When analyzing a cohort of 3,005 patients for 3 years, it was evident that NLR values higher than 3 are associated with high chances of fatal coronary artery disease (OR = 2.45), as well as with the rate of major cardiovascular events (Hazard Ratio - HR = 1.55).<sup>29</sup>

Considering the NLR and the presence of troponin in peripheral blood in the analysis of 244 patients with chest pain treated at the emergency department, a high correlation was found between high NLR and high plasma troponin levels when acute myocardial infarction was confirmed. In those cases in which troponin was positive, the mean NLR was 5.49. On the other hand, negative troponin results showed a mean a NLR of 2.40.<sup>32</sup>

A meta-analysis of 21 studies, including more than 34,000 patients, showed that neutrophilia causes NLR imbalance, favoring the development of cardiovascular

disorders compatible with acute myocardial infarction, unstable angina, acute coronary syndrome, heart failure development or aggravation, cerebrovascular accident, and even increased mortality.<sup>30</sup>

### **Perspectives: association of the neutrophil-lymphocyte ratio with several diseases and need for laboratory reference**

Heart disease pathophysiological processes are associated with the hemodynamic and inflammatory imbalance of other diseases, such as kidney and intestinal diseases.<sup>37,38</sup> For instance, concerning kidney diseases, the mean NLR value of 4.59 in patients submitted to hemodialysis with a diagnosis of atherosclerotic plaques was associated with greater common carotid artery intima-media thickness and higher cardiovascular mortality than patients undergoing hemodialysis but without atherosclerotic plaques, who had a mean NLR of 2.38.<sup>39</sup>

The association between inflammatory bowel diseases such as Crohn's disease and ulcerative colitis and heart disease is probably due to the processes of atherosclerosis and thrombotic events, which lead to an increase in NLR.<sup>40</sup> The imbalance of the lipid profile caused by inflammatory bowel diseases reflects in the decrease of HDL levels and function, in addition to inducing an increase in the levels of LDL, C-reactive protein, pro-inflammatory cytokines, endotoxins, homocysteine and coagulation factors. Therefore, such organic conditions favor endothelial dysfunction, with the onset of the atheroma plaque and other cardiovascular diseases, and an increase in NLR is expected.<sup>41</sup>

Moreover, NLR may be used as a marker of clinical follow-up in cancer cases, which involve significant changes in inflammatory responses concomitantly with the immune system. NLR as a ratio  $\geq 5$  being considered elevated was significantly correlated with larger tumor size in patients with advanced esophageal squamous cell carcinoma than patients with NLR  $< 5$ .<sup>42</sup> The NLR cutoff value  $\geq 5$  also reflected a lower response to Kawasaki disease therapy than patients with NLR  $< 5$ , which is associated with coronary abnormalities.<sup>43</sup> Furthermore, two meta-analyses have also shown that the NLR increase is significantly associated with larger tumor size and lower overall survival in patients with cervical

cancer.<sup>44,45</sup> The NLR was also considered a new prognostic marker in patients with liver cancer.<sup>46</sup>

Due to the importance represented by recent studies regarding NLR in the prognosis for cardiovascular diseases<sup>39,43,47-49</sup> and its association with other inflammatory diseases,<sup>42,44,45,50</sup> establishing a laboratory reference specific for the NLR is promising. Differences in demographic classifications, such as classifications by age group and gender, should be considered.

### **Conclusion**

The genesis of atherosclerotic processes, as well as other diseases associated with inflammatory processes, directly influence the neutrophil/lymphocyte ratio; thus, the NLR emerges as an auxiliary tool mainly in the prognosis of atherosclerosis-related cardiac disorders. The use of this ratio can help the physician to stratify patients into different categories of risk for cardiovascular disease development. It can be easily incorporated into the laboratory routine and it practically does not involve additional costs. However, it is necessary to standardize NLR cutoff points for this type of disorder, as well as in other disease processes.

### **Author contributions**

Conception and design of the research and writing of the manuscript: Santos HO, Izidoro LFM; Acquisition of data and analysis and interpretation of the data: Santos HO; Critical revision of the manuscript for intellectual content: Izidoro LFM.

### **Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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### **Study Association**

This study is not associated with any thesis or dissertation work.

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