REVIEW ARTICLE

Neutrophil-Lymphocyte Ratio in Cardiovascular Disease Risk Assessment

Heitor Oliveira Santos and Luiz Fernando Moreira Izidoro

Universidade Federal de Uberlândia, Uberlândia, MG - Brazil

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.[1,2] 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.[3,4]

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.[4,5]

Keywords

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.[6] 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.[7-9]

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-α).[10] 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.[9]

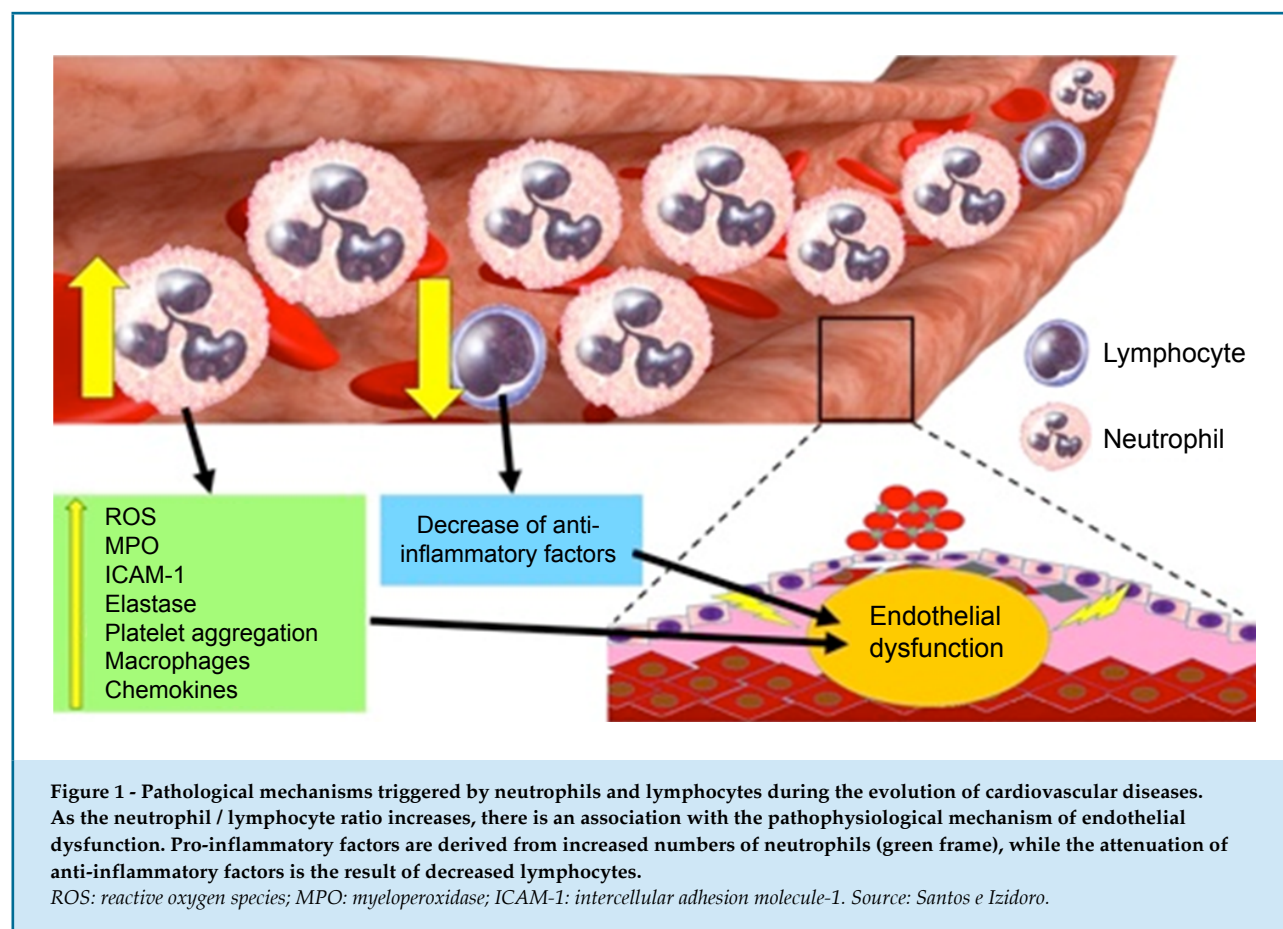On the other hand, mechanisms related to neutrophilia in cardiovascular diseases are more clarified,

Mailing Address: Luiz Fernando Moreira Izidoro
Avenida Pará, 1.720, Umuarama. Postal Code: 38400-902. Uberlândia, MG - Brazil.
E-mail: luiz.izidoro@ufu.br, moreiraizidoro@hotmail.com

Figure 1 - Pathological mechanisms triggered by neutrophils and lymphocytes during the evolution of cardiovascular diseases. As the neutrophil / lymphocyte ratio increases, there is an association with the pathophysiological mechanism of endothelial dysfunction. Pro-inflammatory factors are derived from increased numbers of neutrophils (green frame), while the attenuation of anti-inflammatory factors is the result of decreased lymphocytes.
ROS: reactive oxygen species; MPO: myeloperoxidase; ICAM-1: intercellular adhesion molecule-1. Source: Santos e Izidoro.

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.[11]

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

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.[7,8,20-25] The neutrophil cells, themselves, also express atherogenic factors, such as chemokines and cytokines.[11]

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.[3,11,26]

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 phagocyte the oxidized LDL, forming the foam cells.[11]

Pathological mechanisms originating from neutrophils and lymphocytes during cardiovascular diseases

Epidemiological evidence has shown the predictive role of NLR in atherosclerotic manifestations.[27-30] 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.[27] 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.[11] Based on the interpretation of the NLR results, it is possible to predict the presence of atherosclerotic processes before the coronary angiography is performed.[28,31]

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.[32]

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.[30] Patients with total coronary occlusion also have a higher NLR value, being significantly more pronounced than in patients with normal coronary arteries ($p < 0.001$).[33]

In a study of 194 volunteers with coronary artery disease submitted to coronary angiography,[19] 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).[17]

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.[34] 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).[35]

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).[3] 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).[26]

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.[36]

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).[29]

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.[32]

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.[30]

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.[37,38] 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.[39]

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.[40] 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.[41]

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 ≥ 5 being considered elevated was significantly correlated with larger tumor size in patients with advanced esophageal squamous cell carcinoma than patients with NLR < 5.[42] The NLR cutoff value ≥ 5 also reflected a lower response to Kawasaki disease therapy than patients with NLR < 5, which is associated with coronary abnormalities.[43] Furthermore, two meta-analyzes have also shown that the NLR increase is significantly associated with larger tumor size and lower overall survival in patients with cervical cancer.[44,45] The NLR was also considered a new prognostic marker in patients with liver cancer.[46]

Due to the importance represented by recent studies regarding NLR in the prognosis for cardiovascular diseases[39,43,47-49] and its association with other inflammatory diseases,[42,44,45,50] 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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References

1. Arredondo A, Aviles R. Costs and epidemiological changes of chronic diseases: implications and challenges for health systems. PLoS One. 2015;10(3):e0118611.

2. Deniz S, Şengül A, Aydemir Y, Çeldir Emre J, Özhan MH. Clinical factors and comorbidities affecting the cost of hospital-treated COPD. Int J Chron Obstruct Pulmon Dis. 2016 Dec 2;11:3023-30.

3. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol. 2014;11(5):276-89.

4. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006;113(19):2335-62.

5. Osei-Bimpong A, McLean R, Bhonda E, Lewis SM. The use of the white cell count and haemoglobin in combination as an effective screen to predict the normality of the full blood count. Int J Lab Hematol. 2012;34(1):91-7.

6. Blumenreich MS. The white blood cell and differential count. In: Walker HK, Hall WD, Hurst JW. (editors). Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston: Butterworths; 1990. Chap. 153.

7. Wigren M, Nilsson J, Kolbus D. Lymphocytes in atherosclerosis. Clin Chim Acta. 2012;413(19-20):1562-8.

8. Song L, Leung C, Schindler C. Lymphocytes are important in early atherosclerosis. J Clin Invest. 2001;108(2):251-9.

9. Núñez J, Miñana G, Bodí V, Núñez E, Sanchis J, Husser O, et al. Low lymphocyte count and cardiovascular diseases. Curr Med Chem. 2011;18(21):3226-33.

10. Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annu Rev Immunol. 2012;30:459-89.

11. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. Circ Res. 2012;110(6):875-88.

12. Naruko T, Ueda M, Haze K, van der Wal AC, van der Loos CM, Itoh A, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation. 2002;106(23):2894-900.

13. Kruger P, Saffarzadeh M, Weber AN, Rieber N, Radsak M, von Bernuth H, et al. Neutrophils: between host defence, immune modulation, and tissue injury. PLOS Pathog. 2015;11(3):e1004651.

14. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13(3):159-75.

15. Carvalho LO, Aquino EN, Neves AC, Fontes W. The neutrophil nucleus and its role in neutrophilic function. J Cell Biochem. 2015;116(9):1831-6.

16. Tuttolomondo A, Di Raimondo D, Pecoraro R, Arnao V, Pinto A, Licata G. Atherosclerosis as an inflammatory disease. Curr Pharm Des. 2012;18(28):4266-88.

17. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med. 2013 May 1;11:117.

18. Mason C. Venous thromboembolism: a chronic illness. J Cardiovasc Nurs. 2009;24(6 Suppl):S4-7.

19. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. Curr Pharm Des. 2012;18(11):1478-93.

20. Schuett H, Luchtefeld M, Grothusen C, Grote K, Schieffer B. How much is too much? Interleukin-6 and its signalling in atherosclerosis. Thromb Haemost. 2009;102(2):215-22.

21. Schieffer B, Selle T, Hilfiker A, Hilfiker-Kleiner D, Grote K, Tietge UJ, et al. Impact of interleukin-6 on plaque development and morphology in experimental atherosclerosis. Circulation. 2004;110(22):3493-500.

22. Meletta R, Müller Herde A, Dennler P, Fischer E, Schibli R, Krämer SD. Preclinical imaging of the co-stimulatory molecules CD80 and CD86 with indium-111-labeled belatacept in atherosclerosis. EJNMMI Res. 2016;6(1):1.

23. Lutgens E, Lievens D, Beckers L, Donners M, Daemen M. CD40 and Its ligand in atherosclerosis. Trends Cardiovasc Med. 2007;17(4):118-23.

24. Lievens D, Eijgelaar WJ, Biessen EAL, Daemen MJ, Lutgens E. The multi-functionality of CD40L and its receptor CD40 in atherosclerosis. Thromb Haemost. 2009;102(2):206-14.

25. Hartman J, Frishman WH. Inflammation and atherosclerosis: a review of the role of interleukin-6 in the development of atherosclerosis and the potential for targeted drug therapy. Cardiol Rev. 2014;22(3):147-51.

26. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102(6):653-7.

27. Açar G, Fidan S, Uslu ZA, Turkday S, Avci A, Alizade E, et al. Relationship of neutrophil-lymphocyte ratio with the presence, severity, and extent of coronary atherosclerosis detected by coronary computed tomography angiography. Angiology. 2015;66(2):174-9.

28. Kaya H, Ertas F, Islamoglu Y, Kaya Z, Atilgan ZA, Cil H, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost. 2014;20(1):50-4.

29. Paquissi FC. The role of inflammation in cardiovascular diseases: the predictive value of neutrophil-lymphocyte ratio as a marker in peripheral arterial disease. Ther Clin Risk Manag. 2016 May 27;12:851-60.

30. Nilsson L, Wieringa WG, Pundziute G, Gjerde M, Engvall J, Swahn E, et al. Neutrophil/Lymphocyte ratio is associated with non-calcified plaque burden in patients with coronary artery disease. PLoS One. 2014;9(9):e108183.

31. Uysal HB, Dağlı B, Akgüllü C, Avcil M, Zencir C, Ayhan M, et al. Blood count parameters can predict the severity of coronary artery disease. Korean J Intern Med. 2016;31(6):1093-100.

32. Korkmaz A, Yildiz A, Gunes H, Duyuler S, Tuncez A. Utility of neutrophil-lymphocyte ratio in predicting troponin elevation in the emergency department setting. Clin Appl Thromb Hemost. 2015;21(7):667-71.

33. Demir K, Avci A, Altunkeser BB, Yilmaz A, Keles F, Ersecgin A. The relation between neutrophil-to-lymphocyte ratio and coronary chronic total occlusions. BMC Cardiovasc Disord. 2014;14:130.

34. Aygun F, Efe D. Association of neutrophil/lymphocyte ratio with obstructive coronary artery disease and coronary artery calcium score detected by multislice computed tomography in type 2 diabetes mellitus patients. Patient Prefer Adherence. 2015 Jul 17;9:1023-31.

35. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Neutrophil-to-Lymphocyte Ratio and Its Association with Critical Limb Ischemia in PAOD Patients. Pasterkamp G, editor. PLoS One. 2013;8(2):e56745.

36. Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol. 2011;107(3):433-8.

37. Acarturk G, Acay A, Demir K, Ulu MS, Ahsen A, Yuksel S. Neutrophil-to-lymphocyte ratio in inflammatory bowel disease - as a new predictor of disease severity. Bratisl Lek Listy. 2015;116(4):213-7.

38. Demir AK, Demirtas A, Kaya SU, Tastan I, Butun I, Sagcan M, et al. The relationship between the neutrophil-lymphocyte ratio and disease activity in patients with ulcerative colitis. Kaohsiung J Med Sci. 2015;31(11):585-90.

39. Li H, Lu X, Xiong R, Wang S. High neutrophil-to-lymphocyte ratio predicts cardiovascular mortality in chronic hemodialysis patients. Mediators Inflamm. 2017;2017:9327136.

40. Andersen NN, Jess T. Risk of cardiovascular disease in inflammatory bowel disease. World J Gastrointest Pathophysiol. 2014;5(3):359-65.

41. Schicho R, Marsche G, Storr M. Cardiovascular complications in inflammatory bowel disease. Curr Drug Targets. 2015;16(3):181-8.

42. Zhou XL, Li YQ, Zhu WG, Yu CH, Song YQ, Wang WW, et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for patients with locally advanced esophageal squamous cell carcinoma treated with definitive chemoradiotherapy. Sci Rep. 2017 Feb 14;7:42581.

43. Cho HJ, Bak SY, Kim SY, Yoo R, Baek HS, Yang S, et al. A high neutrophil: lymphocyte ratio is associated with refractory Kawasaki disease. Pediatr Int. 2017;59(6):669-674.

44. Wu J, Chen M, Liang C, Su W. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in cervical cancer: a meta-analysis and systematic review. Oncotarget. 2017;8(8):13400-12.

45. Huang QT, Man QQ, Hu J, Yang YL, Zhang YM, Wang W, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in cervical cancer: a systematic review and meta-analysis of observational studies. Oncotarget. 2017;8(10):16755-64.

46. Liu X, He L, Han J, Wang L, Li M, Jiang Y, et al. Association of neutrophil-lymphocyte ratio and T lymphocytes with the pathogenesis and progression of HBV-associated primary liver cancer. PloS One. 2017;12(2):e0170605.

47. Vakili H, Shirazi M, Charkhkar M, Khaheshi I, Memaryan M, Naderian M. Correlation of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio with thrombolysis in myocardial infarction frame count in ST-segment elevation myocardial infarction. Eur J Clin Invest. 2017;47(4):322-7.

48. Nam SH, Kang SG, Song SW. The neutrophil-lymphocyte ratio is associated with coronary artery calcification in asymptomatic Korean males: a cross-sectional study. Biomed Res Int. 2017;2017:e1989417.

49. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of heart failure. Arq Bras Cardiol. 2015;105(6):606-13.

50. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;10(1):12.