

THE ASSOCIATION BETWEEN NEUTROPHIL AND LYMPHOCYTE RATIO AND EXERCISE CAPACITY AT PATIENTS WITH CARDIOVASCULAR DISEASE

Andrei Drugescu¹, Radu Sebastian Gavril¹, Oana Irina Gavril¹, Teodor Vasilcu¹,
Dan-Alexandru Costache^{1,2}, Răzvan Platon³, Florin Mitu^{1,2}

¹Iași University of Medicine and Pharmacy

²Clinical Recovery Hospital, Iași

³Sf. Spiridon Hospital, Iași.

Corresponding author: andreidrugescu@yahoo.com

Abstract

The neutrophil to lymphocyte ratio (N/L) is an indicator of systemic inflammation and a prognostic marker in patients with several cardiovascular diseases (CVDs). Exercise capacity (EC) plays an important role in predicting morbidity and mortality especially in patients with coronary artery disease and heart failure. Studies have been conducted to evaluate the correlation between N/L ratio and EC in CVDs. We searched the PubMed (MEDLINE) database using the keywords “neutrophil”, “lymphocyte”, “neutrophil to lymphocyte ratio”, “cardiovascular disease”, “exercise capacity” and derivatives. Considering the dispersion of these studies as well as reports on prognostic value of N/L ratio in CVDs, we have summarized these findings as a review article. A significant association between higher N/L ratio and low EC was identified, both of which has predictive and prognostic value especially for patients with heart failure.

Keywords: neutrophil, lymphocyte, cardiovascular disease, exercise capacity.

Rezumat

Raportul neutrofile-limfocite (N/L) este un marker de inflamație sistemică ce are utilitate prognostică la pacienții cu afecțiuni cardiovasculare. Capacitatea de efort are un important rol prognostic în prezicerea morbidității și mortalității la pacienții cu boală coronariană și insuficiență cardiacă. Date despre această relație dintre raportul N/L și capacitatea de efort nu au întârziat să apară în literatura de specialitate, având în vedere spectrul larg de afecțiuni cardiovasculare, pe care le-am sumarizat în această lucrare. Folosind cuvintele cheie “neutrophil”, “lymphocyte”, “neutrophil to lymphocyte ratio”, “cardiovascular disease”, “exercise capacity” și derivate am căutat articole în baza de date PubMed (MEDLINE). Valorile crescute ale raportului N/L au fost asociate cu o capacitate scăzută de efort, ambele entități având valoare prognostică și predictivă, în special la pacienții cu insuficiență cardiacă.

Cuvinte cheie: neutrofile, limfocite, boli cardiovasculare, capacitate de efort



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Introduction

Cardiovascular disease (CVD) is a leading contributor to global mortality and morbidity. Internationally, it is the cause of approximately a third of total yearly deaths, with mortality rates in high-income countries ranging from 20% to 50%. Also CVD are chronic conditions that could impair physical functionality, psychological health and life quality⁽¹⁾. Atherosclerotic cardiovascular disease is one of the most common diseases in Romania^(2,3).

The neutrophil/lymphocyte ratio (N/L ratio) is one of several inflammatory parameters that have been proposed as prognostic markers to determine the systemic inflammatory response. N/L ratio are being widely used for diagnostic and prognostic purposes in various conditions, such as in solid tumors⁽⁴⁾, autoimmune diseases⁽⁵⁾, and infectious disease⁽⁶⁾ and last but not at least cardiovascular diseases. The N/L ratio, which is calculated from a complete blood count, is an inexpensive and easy to obtain marker of inflammation that can aid in the risk stratification of patients with various cardiovascular diseases alongside traditionally used markers⁽⁷⁾.

Exercise capacity (EC) and functional capacity are one of the most important prognostic factors in patients with cardiovascular diseases, which is generally measured indirectly and expressed as metabolic

equivalent (MET) according to the treadmill test. However, the best objective method to determine EC is cardiopulmonary exercise test which measures peak oxygen consumption but this examination is not always available and requires expertise⁽⁸⁾. This paper will review recent updates on the evidence regarding the association of N/L ratio and effort capacity in various cardiovascular diseases.

Research Strategy

For this review, we conducted a search strategy from internationally accepted database - PubMed (MEDLINE), using specific keywords, including neutrophil and lymphocyte ratio and effort capacity. We used a combination of keywords [neutrophil and lymphocyte ratio; neutrophils; neutrophil; lymphocytes; lymphocyte] + [exercise capacity; effort capacity; physical exertion; functional capacity; stress test] + [heart disease; cardiovascular disease; coronary artery disease; chronic coronary syndrome; heart failure; valvulopathy]. Our research included prospective and retrospective cohorts and randomized clinical trials that included patients at whom was evaluated the effort capacity by treadmill test, cardiopulmonary exercise tests (CPET) or 6 minutes walk test (6MWT). Studies with patients under 18 years old, studies that did not mention about effort capacity or functional capacity, or

studies that included other conditions besides cardiovascular disorders were excluded.

N/L ratio is extremely frequently used not only in cardiovascular disease, given it is inexpensive and easy to obtain and we considered it useful to draw attention to its use in estimate the effort capacity, especially in patients with cardiovascular disorders that could be enrolled in rehabilitation programs

Coronary artery disease (CAD)

Exercise capacity, which is assessed based on peak oxygen uptake (peak VO_2), is considered the gold standard for assessing aerobic exercise intensity⁽⁹⁾. Peak VO_2 can also be expressed as metabolic equivalent (MET; $=3.5 \text{ ml/kg per min } \text{VO}_2$) for those patients who cannot be evaluated with CPET.

Kodama et al. observed that participants with a maximal exercise capacity (MAC) of 7.9 METs or more had substantially lower rates of all-cause mortality and CAD events compared with those with a MAC of less 7.9 METs⁽¹⁰⁾.

Okan reported the result of his trial in which evaluated 23 patients with CAD and reported that higher N/L ratios were negatively correlated with MET value and duration of exercise ($p < 0.05$). For all patients were performed symptom - limited treadmill test and 6MWT. The result of 6MWT test distance was $333.43 \pm 86.58 \text{ m}$ and the N/L ratio was 2.01 ± 1.22 ⁽¹¹⁾.

Verdoia et al. recently investigated the relationship between N/L ratio and angiographic defined CAD in over 3000 patients and concluded that, independent of the established cardiovascular risk factors, N/L ratio was associated with the extent of coronary lesions and the complexity of the lesion (calcification, thrombus)⁽¹²⁾.

In a recent trial published in 2017, Korkmaz et al evaluated the role of N/L ratio in addition to

treadmill ECG testing in predicting CAD. All patients underwent a treadmill exercise test by an experienced technician under the supervision of a cardiologist in accordance with the Bruce protocol. 60% percent of patients was positive at treadmill test. Increase of N/L ratio after exercise test was significantly higher in patients with positive exercise test than those with negative exercise test (0.49 ± 0.58 vs 0.19 ± 0.44 , $P = .016$). A cut-off point of 0.2 for the change in the N/L ratio in addition to positive stress test had 91% sensitivity and 92% specificity in predicting significant coronary artery stenosis (AUC:0.913, 95% CI: 0.805-1.000, $P < .001$)⁽¹³⁾.

An observational study in a cohort of patients with CAD demonstrated that atherosclerosis progression correlated with increased N/L ratio [relative risk (RR) 2.267, 95% CI 1.068-4.815, $p = 0.03$]. N/L ratio was also found to be higher in those who had progressive atherosclerosis (5.0 ± 5.1) compared to the nonprogressive group (3.2 ± 3.0 ; $p = 0.001$)⁽¹⁴⁾. In a study of 186 patients who presented with stable angina pectoris, an N/L ratio of above 2.7 was noted to correlate with a high SYNTAX score⁽¹⁵⁾.

In 2015, Okyaky et al evaluated the relationship between N/L ratio and impaired myocardial perfusion in cardiac syndrome X (CSX). Sixty consecutive patients (54.1 ± 7.8 years of age, 49 females) diagnosed with CSX according to the presence of typical exercise-induced angina pectoris, transient ischemic ST-segment depression ($>1 \text{ mm}$) during the treadmill exercise test, and angiographically normal coronary arteries constituted the study group. The total exercise time was 8 to 12 minutes. Thirty-eight patients with CSX (63.3%) had deteriorated myocardial perfusion according to the myocardial blush grade (MBG) scores. When the patients with CSX were divided into two groups according to their myocardial perfusion, patients with



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impaired perfusion had a higher N/L ratio than that of patients with normal perfusion (2.13 ± 0.82 vs 1.71 ± 0.59 , respectively; $p = 0.028$)⁽¹⁶⁾.

Heart failure (HF)

Despite the many advances made in HF diagnosis and treatment, the condition still portends a high morbidity and mortality. The role of inflammation in congestive HF has been previously described. The mechanism postulated is that pro-inflammatory cytokines cause left ventricular systolic dysfunction⁽¹⁷⁾. A study carried out by Uthamalingam et al showed that a higher N/L ratio is associated with higher mortality in HF patients⁽¹⁸⁾.

Çakıcı et al assessed the relationship between N/L ratio and EC of patients with compensated HF. 94 patients undergone symptom-limited treadmill testing. Poor EC was defined as <5 metabolic equivalent (MET) in the exercise test. A cut-off point of 2.74 was established for predicting poor EC. Moreover, patients with N/L ratio >3 had more frequent atrial fibrillation (AF), higher NT-proBNP values, increased left atrial (LA) dimensions and systolic pulmonary artery pressure (sPAP), lower LVEF and more severe left ventricular (LV) diastolic dysfunction⁽¹⁹⁾.

In another study dealing with individuals with idiopathic dilated cardiomyopathy (IDC) diagnosis, the elevated NLR was associated with poor functional capacity. Functional capacity, expressed as MET based on treadmill

test, is one of the major prognostic factors in individuals with heart failure. The NLR value with a threshold level of 2.26 predicts a poor functional capacity with the sensitivity of 83% and specificity of 69%⁽²⁰⁾. In the same cohort, NLR was also correlated to both systolic and diastolic LV dysfunction, independently of the EC⁽²⁰⁾. In patients with IDC, higher NLR values were associated to higher NYHA class and higher BNP levels. NLR was correlated to the severity of chronic HF, a cut-off value of NLR ≥ 2.25 associating 82% sensitivity and 65% specificity to predict severity of the cardiac condition. Parameters of cardiac remodeling, such as LV and LA volumes and dimensions, LV systolic and diastolic function, sPAP and right ventricular systolic motion were significantly impaired in patients with a NLR ≥ 2.25 ⁽²¹⁾.

Other conditions

Valvular heart diseases could be asymptomatic and stress test is usually used to expose the symptoms and stratificate the risk. Unfortunately, no study evaluated the relationship between asymptomatic valvular disease and exercise capacity until the moment of this paper publication. However a correlation has been shown between elevated N/L ratio and mitral annular calcification ($p < 0.001$, $r = 0.58$); N/L ratio is higher in patients with mitral annular calcification (3.3 ± 1.8 vs. 1.6 ± 0.4 , $p < 0.001$) than control individuals⁽²²⁾. N/L ratio has also been found to be significantly

higher in patients with severe aortic stenosis with reduced ejection fraction (EF) (3.94 ± 0.88 , $p < 0.001$) as compared to the group of patients with severe aortic stenosis with preserved EF and cohort of patients with mild-to-moderate aortic stenosis⁽²³⁾.

N/L ratio has been shown that can predict appearance of arrhythmias, especially AF. A retrospective large cohort were annually screened in a tertiary medical center. Subjects were divided into 2 groups based on their baseline N/L ratio: low (< 2.83 ; $n = 17,524$) and high (≥ 2.83 ; $n = 3,594$); and showed that the cumulative probability of incident AF was significantly higher among subjects with high N/L ratio compared with low N/L ratio group ($p = 0.006$)⁽²⁴⁾. Although doesn't studied EC at patient with cardiovascular affections we consider important to mention Sultan's paper in our research because it's one of a small list of trials that evaluated EC by CPET. Patients undergoing major gastrointestinal surgery completed symptom-limited maximal CPET as part of their routine preoperative assessment. Anaerobic threshold (AT) was used as the marker of aerobic fitness. Impaired cardiovascular performance (AT < 11 mL/kg per min, with a median peak VO_2 of 14.8 mL/kg per min) was associated independently with higher N/L ratio ($r = 0.04$) thus poor exercise capacity in patients without a diagnosis of heart failure is independently associated with markers of inflammation⁽²⁵⁾.

Paper limitations

Most of included studies was single-centered and included relatively small number of patients. N/L ratio was the only inflammatory marker evaluated in relation to exercise capacity because of the cost and not immediately available in daily practice of other biomarkers. Simultaneous measurement of other inflammatory markers such as IL-6,

tumor necrosis factor- α and high sensitive C-reactive protein may increase the diagnostic utility of N/L ratio for the prediction of poor exercise capacity. Furthermore, in the assessment of functional capacity CPET was not performed due to the inadequate equipment or was avoided for its complexity. Also, only one study reported a cutoff value of N/L ratio that could predict poor exercise capacity.

Finding a clinically relevant and consistent cutoff for high and low N/L ratio in relationship with exercise capacity and ways to influence N/L ratio in a clinically relevant and beneficial manner (such as cardiovascular rehabilitation programs of anti-inflammatory therapies) are the most significant questions we hope will be answered in the next trials.

Conclusions

A substantive evidence base supports cardiac rehabilitation as a clinically effective and cost-effective intervention for patients with CAD or HF therefore is of utmost importance to identify parameters that can identify poor functional capacity. As an easily accessible parameter, NLR could be used to predict the exercise capacity and functional capacity, to estimate MET value and distance that patients could cover in 6MWT, especially in patients with HF

References

1. Smith S, Chaudhary K, Blackstock F. Concordant Evidence-Based Interventions in Cardiac and Pulmonary Rehabilitation Guidelines. *J Cardiopulmon Rehab Prevent* 2019; 39: 9–18.
2. Townsend N, Wilson L, Bhatnagar P et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016; 37(42):3232-3245.
3. Eurostat. Health in the European Union – facts and figures. Online publications 2017.
4. Demirer Z, Uslu AU. Predictive value of neutrophil-lymphocyte ratio in non-muscle-invasive bladder cancer. *Urol Oncol*. 2016; 34(1):1–2.
5. Li L, Xia Y, Chen C, Cheng P, Peng C. Neutrophil-



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General Reviews

lymphocyte ratio in systemic lupus erythematosus disease: a retrospective study. *Int J Clin Exp Med*. 2015;8(7):11026-31

6. Martins EC, da Fe Silveira L, Viegas K, Beck AD, Júnior GF, Cremonese RV, et al. Neutrophil-lymphocyte ratio in the early diagnosis of sepsis in an intensive care unit: a case control study. *Rev Bras Ter Intensiva*. 2019;31(1):63-70.

7. Yıldız A, Kaya H, Ertaş F et al. Association between neutrophil to lymphocyte ratio and pulmonary arterial hypertension. *Türk Kardiyol Dern Ars* 2013;41:604-9

8. Fleg JL, Pina IL, Balady GJ et al. Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology. American Heart Association. *Circulation* 2000; 102: 1591-1597.

9. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European association for cardiovascular prevention and rehabilitation, the American association of cardiovascular and pulmonary rehabilitation and the Canadian association of cardiac rehabilitation. *Eur J Prev Cardiol* 2013;20(3):442-67.

10. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009.

11. Okan S. The relationship between exercise capacity and neutrophil/lymphocyte ratio in patients taken to cardiopulmonary rehabilitation program. *Bratisl Med J* 2020; 121 (3) 206 - 210.

12. Verdoia M, Barbieri L, Giovine GD, et al. Neutrophil to lymphocyte ratio and the extent of coronary artery disease: results from a large cohort study. *Angiology*. 2016;67(1):75-82.

13. Korkmaz A, Yıldız A, Türker Duyuler P et al. Combination of change in hematological parameters with exercise stress test to predict coronary artery disease. *J Clin Lab Anal*. 2018 Jan;32(1):e22205.

14. Kalay N, Dogdu O, Koc F, et al. Hematologic

parameters and angiographic progression of coronary atherosclerosis. *Angiology*. 2012;63:213-217.

15. Kaya A, Kurt M, Tanboga IH, et al. Relation of neutrophil to lymphocyte ratio with the presence and severity of stable coronary artery disease. *Clin Applied Thrombosis/Hemostasis*. 2014;20:473-477.

16. Okyay K, Yilmaz M, Yildirim A, Eroglu S et al. Relationship between neutrophil-to-lymphocyte ratio and impaired myocardial perfusion in cardiac syndrome X. *European Review for Medical and Pharmacological Sciences*. 2015; 19: 1881-1887

17. Prabhu SD. Cytokine-induced modulation of cardiac function. *Circ Res*. 2004;95:1140-1153.

18. Uthamalingam S, Patvardhan EA, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. *Am J Cardiol*. 2011;107:433-438.

19. Cakici M, Cetin M, Dogan A et al. Neutrophil to lymphocyte ratio predicts poor functional capacity in patients with heart failure. *Arch Turk Soc Cardiol* 2014; 42(7):612-620.

20. Yildiz A, Yüksel M, Oylumlu M, Polat N, Akil MA, Acet H. The association between the neutrophil/lymphocyte ratio and functional capacity in patients with idiopathic dilated cardiomyopathy. *Anatolian J of Cardiology* 2015; 15: 13-17.

21. Avci, A, Alizade E, Fidan S, Yesin M, Guler Y. Neutrophil/lymphocyte ratio is related to the severity of idiopathic dilated cardiomyopathy. *Scand Cardiovasc J* 2014; 48(4):202-8.

22. Varol E, Aksoy F, Ozaydin M et al. Association between neutrophil-lymphocyte ratio and mitral annular calcification. *Blood Coagul Fibrinolysis*. 2014;25:557-560.

23. Avci A, Elnur A, Göksel A et al. The relationship between neutrophil/lymphocyte ratio and calcific aortic stenosis. *Echocardiography*. 2014;31:1031-1035.

24. Berkovitch A, Younis A, Grossman Y et al. Relation of Neutrophil to Lymphocyte Ratio to Risk of Incident Atrial Fibrillation. *Am J Cardiol*. 2019 Feb 1;123(3):396-401.

25. Sultan P, Edwards MR, Gutierrez del Arroyo A et al. Cardiopulmonary exercise capacity and preoperative markers of inflammation. *Mediators Inflamm*. 2014;2014: 727451.