

Neutrophil lymphocyte ratio as an inflammatory marker

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Abstract

Neutrophil lymphocyte ratio has been gaining attention as a diagnostic and prognostic tool in various diseases. The test is easy to perform and cost effective. The present review is an effort to survey some of the experimental studies using Neutrophil lymphocyte ratio as one of the important parameter is a reliable marker of inflammation like any other acute phase reactants. The present review is an effort to throw light on what is NLR, its normal range, clinical uses as diagnostic and prognostic marker and its limitations.

Keywords: CRP, neutrophil lymphocyte ratio

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Introduction

The neutrophil lymphocyte ratio has been gaining increasing attention across many fields of medicine for the past 5 years. NLR is used as a marker of subclinical inflammation. It is calculated by dividing the number of neutrophils by number of lymphocytes, usually from peripheral blood.⁴⁷ Physiologically stress increases the number of neutrophil, while decreasing the number of lymphocyte. The NLR combines both these changes. It is a more sensitive reliable index. Hence increased NLR = increased neutrophil /decreased lymphocytes is a marker of stress and acute inflammation. Endogenous cortisol and catecholamines may be major drivers of stress and inflammation. Increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte count.³³ Endogenous catecholamines (epinephrine) may cause leukocytosis and lymphopenia.⁷ NLR is not solely an indication of infection or inflammation.

Interpretation of NLR depends on clinical correlation. Normal NLR is roughly 1-3. An NLR of 6-9 suggests mild stress. Critically ill patients have an NLR of more than 9. Predictive value of NLR is comparable to various other inflammatory markers such as C – reactive protein (CRP), tumor necrosis factor (TNF- α) and interleukin (IL-6) in the detection of subclinical inflammation and endothelial dysfunction in various clinical studies.^{34,42}

Experimental studies

C reactive protein and NLR

It is widely accepted that inflammation contributes to the initiation and progression of cancer.³¹ Simple routine biochemical and hematological markers such as neutrophil to lymphocyte ratio and C- reactive protein might represent host immune responsiveness. Both high NLR as well as high CRP may reflect an inflammatory response to the tumor. It is known that inflammatory processes almost always accompany cancer and

persistence of inflammation – like processes within cancer tissue causes suppression of antitumor immunity by several mechanisms, such as activation of type 2 T- helper responses, recruitment of regulatory T-cells and activation of chemokine system and results in promotion of cancer growth and metastasis.^{31,40} Thus inflammation may result in the aggressive growth of a tumor, and it is considered that high NLR and CRP could be a marker of production of acute inflammatory cytokines by the tumor. The cytokines interleukin-6 and tumor necrosis factor – alpha, which are implicated in the pathogenesis of cancer – related inflammation as well as of acute inflammatory processes, are also known to induce high NLR.⁴³⁻⁴⁵ These markers might be used to stratify patients in the context of chemotherapy trials, in addition to more traditional means such as radiological staging. They might also have role in measuring response to treatment. Pro-inflammatory markers could also be used as a target for intervention rather than just a monitoring tool.³⁰

Gastrectomy is the cornerstone treatment for patients suffering from localized gastric cancer.³⁶ Almost 40 % of gastric cancer patients relapse within 2 years after gastrectomy. Combination of CRP and NLR can help us to predict recurrence ahead and make decisions in the management of Gastric Cancer patients.²² Furthermore, this offers the opportunity to individualize treatments by identifying patients with worse prognosis and a closer follow-up or receive modified adjuvant therapy.

Neutrophil lymphocyte ratio and platelet lymphocyte ratio in SLE

Neutrophil lymphocyte ratio and platelet lymphocyte ratio in peripheral blood are simple systemic inflammatory response markers and showed that NLR possesses a diagnostic value in certain pathologies characterized by systemic or local inflammatory response.⁹ It was also found that NLR was significantly higher in SLE than normal subjects.² Another study found that NLR is independently associated with SLE and showed a significant increase in Lupus nephritis patients.²⁵ In

yet another study it was observed that NLR was increased in lupus nephritis in comparison with SLE without nephritis.⁶ They stated that NLR could reflect inflammatory response and disease activity in SLE patients. Another study reported that NLR was increased in SLE patients in comparison to control. Their study concluded that Neutrophil lymphocyte ratio and platelet lymphocyte ratio can be used as diagnostic markers of SLE and NLR can be used as activity marker in active lupus patients.⁴⁸

NLR and coronary artery disease

Atherosclerosis is a complex inflammatory disease.³⁷ Inflammation plays a major role in all stages of coronary artery disease.¹⁵ Coronary artery is the leading cause of mortality and morbidity throughout the world.^{26,32} White blood cell count and its subtypes have been studied as inflammatory biomarkers to predict adverse cardiovascular outcomes.^{14,17} Neutrophil to lymphocyte ratio (NLR) has recently emerged as new prognostic marker.¹³ A number of studies have suggested that NLR was associated with adverse outcomes in patients undergoing coronary angiography, in those with stable and unstable CAD and also in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting.^{11,12,35} It was demonstrated that patients with abnormal CAG had significantly higher NLR compared to patients with normal CAG.²¹ Moreover, NLR was correlated with severity of CAD. NLR was an independent predictor of CAD. Another study reported that use of combination of NLR and hemoglobin provided valuable information for early risk stratification in patients with ST elevation myocardial infarction (STEMI). Patients with higher NLR and anemia had higher mortality rate at six months compared to patients with lower NLR and without anemia.¹⁰

NLR and Diabetes mellitus

The burden of diabetes is on the rise in middle and lower income countries due to strong influence of urbanization, sedentary life style, nutritional and epidemiological transition.¹⁸ Studies have shown that increased leukocyte counts are reliable

markers of systemic inflammation and have diagnostic as well as prognostic value in patients of angina, myocardial infarction, stroke, peripheral vascular disease and micro and macro vascular complication associated with diabetes.^{29,41} Systemic inflammation has also been attributed to the development of cognitive impairment in diabetes mellitus.³⁸ HbA1c is a widely available test which is usually advised by most clinicians to measure the long term glycemic control in diabetic patients over the period of previous 2-3 months. HbA1c also tells about the severity of hyperglycemia and considered to be a biomarker of risk factors for diabetes related micro and macro-vascular complications.²⁸ However HbA1c usually do not predict ongoing inflammation and diabetes associated complications which are more precisely done by NLR.

Studies have shown that NLR has strong diagnostic as well as prognostic potential for atherosclerosis related vascular diseases in which diabetes mellitus is one of them.^{8,16} It was also revealed that increased NLR has strong association with glucose intolerance and insulin resistance in type 2 diabetic patients.^{27,39} Regarding diabetes related micro vascular complications studies showed that NLR has a reliable predictive marker of early stage diabetic nephropathy, retinopathy and diabetic foot ulcer.^{46,23} Moreover increased NLR is predictor of major cardiovascular events in both acute coronary syndrome and coronary artery disease patients and is also associated with increased carotid artery intima-media thickness in type 2 diabetic patients.^{3,24} Even patients with increased NLR but normal TLC count could have increased risk of atherosclerosis related diseases.^{4,5,20}

Limitations

As there is no consensus regarding NLR cutoff or the method employed to calculate NLR, the values vary among studies. Additionally, there was significant heterogeneity among studies. Other limitations included the retrospective nature of several articles and the lack of descriptions of underlying diseases or concomitant infection that could somehow affect NLR status

Conclusion

NLR has various advantages over other inflammatory markers because of its wide availability, low cost, reliability, easy lab detection. Moreover NLR can be used as screening tool for disease and drug monitoring on large scale basis. It can be used not only as a prognostic factor but also to identify the patients who are prone for complications. In diabetic patients it is more cost effective than HbA1c. It should be recommended in diabetic patients in routine clinical setting not for glycemic control but for prediction of diabetes related complications in future so that effective measures could be taken in order to prevent these complications. NLR can be used as biomarker of CAD since we can detect in the blood easily and early to predict future cardiovascular risk. NLR is also used for the diagnosis of acute exacerbation of COPD and to assess the prognosis in breast cancer patients.

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