

# **The Neutrophil to Lymphocyte Ratio: An Emerging Diagnostic Biomarker for Parainflammation**

## **Abstract**

The present century health care system has made great innovations for the diagnosis and treatment of diseases. Despite this, the diagnosis of parainflammation is difficult due to absence of symptoms in individuals. The development of diseases could generally be mitigated by early detection and control of parainflammation since it appears to be a unifying factor for infectious and non-infectious diseases. The present review describes the value of the neutrophil to lymphocyte ratio as a biomarker for the detection of parainflammation in disease asymptomatic (apparently healthy) individuals.

**Keywords:** Parainflammation, Disease, Apparently Healthy Persons, Neutrophil to Lymphocyte Ratio, Biomarker, Diagnosis

## **Introduction**

Parainflammation is a phenomenon that describes a persistent asymptomatic abnormal immune response during the early stages of disease development which results in breakdown of the host tolerance to the disease (1,2). It is a unifying factor in the process of development of all diseases whether infectious or non-infectious. Although persistent or intermittent body pain, myalgia, arthralgia, chronic fatigue, depression, anxiety, constipation, diarrhea, weight gain or loss has been identified by some scientists as an early sign of parainflammation, they are not constitutive in describing the onset or presence of parainflammation due to the fact that these are common experience after our daily hustles and puzzles(3).

## **Parainflammatory Theory of Diseases**

Parainflammation appears to be a grand unifying factor predisposing apparently healthy persons to diseases(4). Apparently healthy individuals do not present with clinical symptoms for a disease with symptoms being a later occurrence for disease development process and could reduce the degree of reversibility though could be detected with appropriate diagnosis (5,6,7). The disease process begins with the appropriate exposure to or accumulation of factors sufficient for the host susceptibility (7). For an infectious disease, the exposure is a microbial pathogen while for a non-infectious disease, the exposure could be a factor initiates a vicious cycle in the body biological process(5,6). Such exposure leads to an early undetected pathological changes in the body which maybe systemic and/or localized and is referred to as the subclinical disease state (parainflammation) extending from the time of exposure to the onset of disease clinical symptoms usually referred to as the incubation period for infectious diseases and the latency period for non-infectious diseases. The onset of clinical symptoms therefore marks the progression from parainflammation to a disease state with most diagnosis made

during overt disease. This suggests that the diagnosis of parainflammation in healthy individuals and its control provides a target for prevention of the development of diseases.

### **Laboratory Parameters for Investigation of Parainflammation**

The diagnosis of increased neutrophil to lymphocyte ratio may not be specific to any particular disease condition because parainflammation is not a specific disease condition but a pathological process to many diseases though it has been established in many diseases including cardiovascular disease, rheumatic diseases, diabetes mellitus, systemic diseases, colorectal, gastric, lung and ovarian cancer as well as infectious diseases(10). Therefore there is a need to establish a differential diagnosis that could support a definitive diagnosis for parainflammation. In doing this, patients history and physical examination becomes an important initial step to diagnosis. The diagnostic findings may include abnormal immunohematological parameters from the routine full blood count estimations such as an increased serum common cytokines involving but not limited to IL-8, IL-1, IL-6 and TNF- $\alpha$ , increased antinuclear antibodies, rheumatoid factor, amyloid A,C-reactive protein and concomitant hypoalbuminemia as well as polyclonal gammopathy ( gammaglobulin) in serum electrophoresis (2,3,8,9).

### **The Significance of the Neutrophil to Lymphocyte Ratio in the Investigation parainflammation**

The neutrophil to lymphocyte ratio (NLR) is the count ratio of the peripheral blood number of neutrophils and lymphocytes that could be easily calculated by using either absolute cell counts or percentages (10). This ratio gives a multifactoral insight into immunocompetent leukocyte population namely the neutrophil ( granulocytes ) for the innate immune system and lymphocyte (agranulocytes) for the adaptive immune system due to illness and various pathological state (10). The dynamic of the NLR reveals the intensity of immune-inflammatory reaction and the balance between acute and chronic inflammation(11,12,13,14).Previous studies had found significant association of the neutrophil to lymphocyte ratio with established inflammatory markers such as the C-reactive protein and many proinflammatory cytokines supporting the NLR as a useful marker of inflammation(15,16,17,18).

### **Conditions that affects the Neutrophil to Lymphocyte Ratio**

High NLR occurs when the neutrophil count becomes high while the lymphocyte count becomes low whereas a low NLR occurs when the neutrophil count becomes low and the lymphocyte count becomes high. The NLR may not specifically be an indication for parainflammation but may also increase rapidly following acute physiologic stress (<6hours) resulting from any condition that causes physiological stress such as exercise or hypovolemic shock. During physiological stress, the number of neutrophils increases while the number of lymphocytes decreases response to a non pathological increase in the levels of emergency hormones such as cortisol and epinephrine. High levels of cortisol have been identified to cause a concomitant increase in the neutrophil counts while also decreasing the lymphocyte counts. Likewise endogeneous catecholamines such as epinephrines may cause lymphopenia(19). This prompt response time makes the NLR a better reflection of acute stress than parameters such as the complete blood count which are more sluggish to respond parainflammation as well as acute phase reactants which are more labor intensive(10,20,21). The normal range for the NLR is 1-2, values higher than 2.0 or

below 1.0 in adults may be diagnostic of a condition. An NLR greater than 2 is an early sign of a pathological process such as parainflammation (10). Values 3-7 indicates mild parainflammation, 7-11 indicates moderate parainflammation and sepsis, 11-17 indicates severe parainflammation while 17-23 indicates septic shock and multiple trauma while an NLR  $\geq 23$  indicates terminal cancer. The elevation of NLR has relation to the worsening of clinical course, similarly the decrease is related to an improvement or good prognosis(10).

## Conclusion

The NLR has been shown to be an accurate, cheap and easy diagnostic marker for parainflammation. The current use of the white blood cell as a clinical marker for parainflammation is based on the fact that it is available and easy to determine. However, given the availability of the NLR, using it to replace the white blood cell count seems like a natural evolution with a better diagnostic and prognostic insight for parainflammation. It is also less expensive compared to the labor and cost of determination of other markers of parainflammation such as lactate, procalcitonin, albumin etc.

## References

1. Castro AM, Concha MLE, Melendez CAP (2017). Low grade inflammation and its relation to obesity and chronic degenerative disease. *Special Issue on Genetics* 80:101-105
2. Needham EJ, Helmy A, Menon DK (2019). The immunological response to traumatic brain injury. *Journal of Neuroimmunology* 15:112-125
3. Dinh KM, Kaspersen KA, Mikkelsen S, Pedersen OB, Petersen MS, Thorner LW, Hjalgrim H, Rostgaard K, Ullum H, Erikstrup C (2019). Low grade inflammation is negatively associated with physical health-related quality of life in healthy individuals: results from the Danish Blood Donor Study (DBDS). *Public Library of Science One* 14:e0216339
4. Ogbuabor AO, Nwobodo HA, Chukwurah FE (2022) Parainflammation : an immunohematological risk factor for the emergence and re-emergence of diseases. *Journal of Immunology Research and Reports* 2(3):1-2
5. Ronnback C, Hansson E (2019). The importance and control of low grade inflammation due to damage of cellular barrier systems that may lead to systemic inflammation. *Frontiers in Neurology* 10:533
6. Plytycz B, Seljelid R (2003). From inflammation to sickness: historical perspective. *Archives of Immunology Therapy Experts* 51:105-109
7. Nissen-Meyer LSH, Seghatchian J (2019). Donor health assessment - when is blood donation safe? *Transfusion and Apheresis Sciences* 58:113-116
8. Tsai DH, Reidiker M, Berchet A, Paccaud F, Waeber G, Vollenweider P, Bochud M (2019). Effect of short- and long- term exposures to particulate matter on inflammatory markers levels in the general population. *Environmental Science Pollution Research International* 26:19697-19704

9. Pahwa R, Royal A, Bansal P, Jialal L (2022).Chronic inflammation in : Stat Pearls [Internet] Treasure Island (FL); Stat Pearls Publishing.
10. Ngo TQ, Truong MH (2022).Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, novel biomarkers and applications in urology : an update. *Journal of Regenerative Biology and Medicine* 4(3):1-11
11. Song M, Graubard BI, Rabkin CS, Engels EA(2021). Neutrophil-to-lymphocyte ratio and mortality in the united states general population. *Scientific Reports*,11(464):1-9
12. Uduagbamen PK, Oyelese AT, Yusuf AAO, Thompson MU, Alalade BAA, Ehioghae O(2022). Neutrophil lymphocyte ratio as an inflammatory marker in chronic kidney disease : determinants and correlates. *Open Journal of Nephrology* 12:23-35.
13. He X, Qi S, Zhang X, Pan J(2022).The relationship between the neutrophil-to-lymphocyte ratio and diabetic retinopathy in adults from the united states: results from the National Health and Nutrition Examination Survey. *BMC Ophthalmology* ,22(346):1-8
14. Kara SP, Altunan B, Unal A(2022). Investigation of the peripheral inflammation(Neutrophil-lymphocyte ratio) in two neurodegenerative diseases of the central nervous system. *Neurological Sciences* ,43:1799-1807
15. Lubis HH, Lubis HW, Kembaren T(2021). Relationship between neutrophil lymphocyte ratio(NLR) and anxiety levels among covid-19 patients at Adam Malik General Hospital Medan. *International Journal of Research and Reviews*, 8(12):378-383
16. Rinaldi FX, Lembar S, Ridjab DA, Leonardo, Lauryn J, Erlina SGG(2021). Correlation between neutrophil to lymphocyte ratio(NLR) and patients with heart failure: hematology variables in patients with heart failure. *Sriwijaya Journal of Medicine*,5(1):10-17.
17. Demir M (2021). Does inflammation play a role in the pathophysiology of tinnitus? *Nigerian Journal of Clinical Practice*, 24:199-204
18. Rathod BD, Amle D, Khot RS, Prathipati KK, Joshi PP(2022).Neutrophil to lymphocyte ratio as a predictor of disease severity and mortality in coronavirus disease 2019:prospective study from central India. *Cureus*, 14(3):e23696
19. Buonacera A, Stancanelli B, Colaci M, Malatino L (2022). Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. *International Journal of Molecular Sciences* 23(3636):1-10.
20. Ljungstrom L, Pernestg A, Jacobsson G, Anderson R, Usener B, Tilevik D (2017) Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein and lactate in patients with suspected bacterial sepsis. *Public Library of Science* 12(7):e0181704.

21. Suhartono, Wijaya I, Dalimoenthe NZ (2021). The correlation of neutrophil to lymphocyte ratio(NLR) and monocytes to lymphocyte ratio (MLR) with disease severity in hospitalized patients with coronavirus disease 2019(covid-19).Bali Medical Journal,10(2):653-658.

UNDER PEER REVIEW