

Physiological Implications of Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease

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Abstract

Objectives: To determine the physiological significance of Neutrophil-to-Lymphocyte Ratio in inflammatory responses and clinical outcomes of COPD.

Methodology: A case control study that was conducted at Medicine Department of Muhammad Medical College Mirpurkhas, Pakistan, from April 2022 to June 2022. All the patients aged 40 years and above, both gender, clinically diagnosed as patients of COPD and healthy individuals without pulmonary or systemic inflammatory conditions (controls) were included. A 5ml blood sample was obtained from each case and immediately was send to diagnostic laboratory for complete blood count test to assess the neutrophils and lymphocytes. Data was analyzed using GraphPad Prism 9 software, with statistical significance determined by Fischer's exact test ($p \leq 0.05$).

Results: The average age of the case group ($n = 150$) was 59 years, while the control group was around 53 years old. 83.33% of the COPD participants had an NLR greater than 3, and 16.67% had an NLR less than 3. The p-value of 0.0001 indicates a statistically significant difference between the groups. The odds ratio was 0.07027.

Conclusion: A significant relationship was observed between an elevated Neutrophil-to-Lymphocyte Ratio (NLR) and COPD, with COPD patients showing higher neutrophil levels compared to the general population. Easily evaluated and with strong association with disease progression, NLR can serve as an effective marker for routine clinical assessments in COPD patients.

Keywords: COPD, NLR, Severity, Correlation

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Introduction

Chronic obstructive pulmonary disease (COPD) is now becoming the most prevalent respiratory disease days and become the 3 most common cause of high mortality rates worldwide.¹ the main pathophysiology of COPD includes the slowly progressive obstruction of airways along with loss of elastic property of the lungs that leads to limitation of expiratory flow limitation and hyperinflation of lungs that worsen the symptoms of patients.² the prevalence of COPD is increasing as time passes, According to researches the COPD is the sole cause of deaths of 3.23 million population in 2019 and its prevalence in people with age above 40 years become 13.2% that become roughly 67% more than previous prevalence rate of COPD in the same age group 10 years ago.³ It affects 11% population with ages more than 40

years in Spain and affects the normal lifestyle of those individuals.⁴ there are many causes of COPD but the most prevalent cause worldwide is smoking that increase the intracellular ca^{+} levels that in turn enhances the response of smooth muscles present in the airways to muscuarnic agonist and it also increase the oxidative stress of cell that further lead to inflammation of airways and finally culminate to progressive narrowing of airways and hyperinflation of lungs.⁵⁻⁶ there is vasculature abnormality present in the COPD that occur due to damage to microvasculature that supply's the muscles of airways by narrowing of vessels due to deposition of extra cellular matrix proteins and proliferation of smooth muscle cells in response to alveolar injury that further detoriate COPD.⁷

There is limited amount of data available in regards to inflammatory biomarker in COPD but as researches advances there is most reliable and easily assessable biomarker named Neutrophil-Lymphocyte Ratio (NLR) has been introduced that plays an pivotal role in pathogenesis of COPD because the levels of neutrophils and lymphocytes altered during the inflammatory phase

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of COPD that could be used as early indicator that rise during the process and that in turn help in early detection of people who are more prone to this disease.⁸⁻⁹ NLR is not only elevated in COPD but also seen that its levels are highly elevated in other inflammatory diseases like pneumonia, congestive cardiac failure, Pancreatitis, etc. so now its levels are also used as a prognostic marker in inflammatory conditions.¹⁰ The normal levels of neutrophil-lymphocyte ratio vary from one population to another but its average is about 0.78 and 3.0 in health and having no disease, women have lower levels of NLR than males due to hormonal action of estrogen.¹¹ Other blood parameters are elevated in COPD besides NLR that includes platelets-lymphocyte ratio (PLR), Monocyte-Lymphocyte Ratio (MLR) and C-reactive proteins that are also reliable inflammatory Biomarkers that can be used besides NLR.¹²⁻¹³ However this study has been done to evaluate the physiological implications of Neutrophil-to-Lymphocyte Ratio in patients with chronic obstructive pulmonary disease. A local-level research on the physiological implications of NLR in COPD would provide significant insights regarding the unique characteristics of the target population, to enhance the healthcare resource usage, and allow for the creation of more targeted prevention and treatment strategies.

Methodology

It was a case-control study that was conducted from 01-04-2022 to 30-06-2022 at the Department of Muhammad Medical College Mirpurkhas, Sindh, Pakistan. This study was approved by the ethical committee of the department of Physiology and MLT of the University of Sindh, Jamshoro. The sample size of this study was 400 participants, which were divided into two groups for convenience: the control group, which consisted of 250 participants, and the case group, which consisted of 150 participants. All the patients aged 40 years and above, both gender, clinically diagnosed as patients of COPD and healthy individuals without pulmonary or systemic inflammatory conditions (controls) were included. Individuals with history of autoimmune diseases, cancer, acute infections, cardiovascular diseases, cases with smoking history and cases with history of usage of systemic steroids or immunosuppressive drugs within the last 3 months were excluded. Written informed consent was obtained from all the cases. Function of lungs was assessed using standard spirometry tests, including the

measurement of Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC). A 5ml venous blood samples of all participants were carefully collected by an expert nurse using the K2 EDTA tubes and then sent for analysis to perform a Complete Blood Count (CBC), to provide information on the absolute neutrophil and lymphocyte counts, which were used to calculate the Neutrophil-to-Lymphocyte Ratio (NLR). NLR was derived by dividing the absolute neutrophil count by the absolute lymphocyte count, both of which were expressed in cells per microliter (μL). Elevated NLR values were interpreted as markers of systemic inflammation, with the potential to reflect COPD severity and progression. NLR (neutrophil-lymphocyte ratio) was calculated by using CMC per individual. NLR <3 was considered as a better prognosis in patients, with a lower inflammation linked to more stable health conditions and less aggressive disease progression, while NLR value greater than 3 considered a higher level of systemic inflammation, often linked to more severe or advanced disease condition. Data for demographics and clinical characteristics were collected from every participant using study proforma. The results were analyzed SPSS version 23. Fischer's exact test was applied to deduce the P-value, which was considered significant at ≤ 0.05 .

Results

The average age of the case group ($n = 150$) was 59 years, while the control group was around 53 years old. BMI is similar between the two groups, with an average of 24.27 in the case group and 24.36 in the control group. The systolic blood pressure is slightly higher in the case group, with a mean of 175.1 mmHg compared to 143.9 mmHg in the control group. Neutrophil counts were also higher in the case group with a mean of 6.42 than in the control group with a mean around 5.46. Conversely, lymphocyte counts are lower in the case group (1.51) compared to the control group (1.77). Average platelet counts were slightly higher in the case group (207.9) compared to the control group (202.6). (Table I)

Among the normal participants, 26% had an NLR greater than 3, while 74% had an NLR less than 3. In contrast, 83.33% of the COPD participants had an NLR greater than 3, and 16.67% had an NLR less than 3. The p-value of 0.0001 indicates a statistically significant difference between the groups. The odds ratio was 0.07027.

Sensitivity was 34.21%, specificity was 11.90%, and the likelihood ratio was 0.3883. (Table II)

Table I: Demographic Data Of Study Population.

Parameters	Control (n=250)	Case (n=150)	p-value
Age	53.45±12.08	59.23±8.098	0.0001
BMI	24.36±1.356	24.27±1.474	0.5496
Systolic BP	143.9±11.65	175.1±38.73	0.0001
Neutrophil	5.460±0.4718	6.420±0.5608	0.0001
Lymphocytes	1.770±0.1800	1.510±0.1586	0.0001
Platelets	202.6±4.630	207.9±6.823	0.0001

showed that NLR greater than 3 is significantly associated with COPD, with a P-value of 0.0001 and an odds ratio of 3.8.¹⁴ The meta-analysis conducted by Wang Y, Liu Y, et al., which analyzed 15 studies and involved 6783 participants, found that COPD is significantly associated with a higher NLR with a value of < 0.0001.¹⁵ The retrospective cohort study of Kang J, Xu B, et al. delineated the significant association between the frequency of acute exacerbations in COPD patients and elevated levels of NLR with an odds ratio of 3.7.¹⁶

Table II: Comparison Of Neutrophil-To-Lymphocyte Ratio (NLR) Between Normal Participants And Those With Chronic Obstructive Pulmonary Disease (COPD)

PARAMETERS	NLR more than 3	NLR less than 3	P-value	Odds ratio	Sensitivity & specificity	Likelihood Ratio
Normal Participants (n=250)	65 (26.00%)	185 (74.00%)				
Participants with COPD(n=150)	125 (83.33%)	25 (16.67%)	0.0001	0.07027	0.3421 & 0.1190	0.3883
TOTAL	190	210				

Discussion

COPD is a debilitating condition marked by persistent airflow limitation and inflammation that is not easily reversible. The neutrophil-to-lymphocyte ratio (NLR) in peripheral blood has gained attention as a systemic inflammatory marker due to its quick, accessible, and cost-effective measurement through routine blood tests.

In recent years, NLR has been explored as both a diagnostic and prognostic tool in the management of COPD. This study delineates the relationship between raised levels of NLR and patients with chronic obstructive pulmonary disease. The study results show that the sample size for this study was 400 participants, with a distribution into a case group of 150 participants and a control group of 250 participants. Among the control group, about 26% of the population showed a raised NLR of more than 3. In comparison, the case group showed that up to 83.33% of patients affected by chronic obstructive pulmonary disease raised their NLR, i.e., more than 3, compared to a normal individual. This is further supported statistically by the P value of 0.0001, which shows that this relationship is statistically significant. That is also supported by an odds ratio of 0.07 and a likelihood ratio of 0.39. These findings are consistent with studies conducted in previous years. Wang Z et al. conducted a retrospective study and

The multicenter study conducted by Liu J, Tang W, et al. also reported that the severity of COPD is significantly associated with elevated NLR with a p-value of 0.0001.¹⁷

The case-control study results of Chen Z, Wang H, et al. showed the presence of a significant association between NLR and COPD, with an odds ratio of 3.8 and a CI of about 2.9–4.9.¹⁸ However, a different group of studies also opposes these findings and shows no significant association between these two entities. A study conducted by Brown R, Breen E, et al. showed no significance in the association of raised NLR with COPD, with a p-value of 0.15.¹⁹ The study of Huang Z, Zhang Y, et al., Chen X, Wang Y, et al., and Gao H, Xu X, et al. indicates that NLR is not a suitable and reliable marker for COPD, with P values of 0.30, 0.75, and 0.25, respectively.²⁰⁻²² As NLR found to be reliable marker of systemic inflammation, which is central to COPD pathophysiology, its correlation with COPD severity, acute exacerbations, and overall prognosis makes it a valuable clinical tool. It is derived from routine blood tests, making it accessible, cost-effective, and easy to implement in clinical practice, particularly in resource-limited settings. Assumed the chronic and progressive nature of COPD, the quick identification of inflammatory markers like NLR can help tailor treatment plans and predict patient outcomes more efficiently. Although NLR

can be influenced by other conditions involving systemic inflammation, such as infections or autoimmune diseases, this may limit its specificity for COPD. As several studies exploring NLR in COPD are cross-sectional, meaning they capture data at a single point in time. Longitudinal studies are needed to assess the value of NLR as a marker throughout the disease course. Future research should adopt a longitudinal design to track NLR changes over time, especially during COPD exacerbations and remission phases, to better understand its role in disease progression.

Conclusion

As per the study conclusion there was observed a significant relationship between elevated Neutrophil-to-Lymphocyte Ratio (NLR) and COPD, with COPD patients exhibiting higher neutrophil levels compared to the general population. Due to its simplicity in measurement and strong association with disease progression, NLR can be an effective marker for routine clinical assessments in COPD patients. However, the study has certain limitations, including a limited sample size and being conducted in a single hospital, which restricts the generalizability of the results to the broader population. Additionally, the presence of confounding variables may have influenced the outcomes. Future research with larger, multi-center studies is recommended to validate these findings and address these limitations

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