Open Access

Original Article

Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease Exacerbators presenting to Emergency: A Marker of Disease Severity and Poor Outcomes

Muhammad Mahad Qureshi, Muhammad Nadeem Ashraf, Sobia Mariam, Syed Muhammad Hassan Kazmi, Muhammad Farrukh Habib*, Wajid Ali

Department of Emergency Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,
*Department of Community Medicine, Alhamd Islamic University, Islamabad Pakistan

ABSTRACT

Objective: To determine the predictive value of Neutrophil-to-Lymphocyte Ratio in COPD Exacerbation as a marker of disease severity and poor outcomes.
Study Design: Prospective longitudinal study.
Place and Duration of Study: Department of Emergency, Pakistan Emirates Military Hospital, Rawalpindi Pakistan, from Dec 2022 to Jun 2023.
Methodology: 150 patients with severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease were enrolled in the study. Convenience sampling was performed. Patients were divided into 3 groups based upon value of Neutrophil to Lymphocyte ratio with 50 patients in each group. Neutrophil to Lymphocyte ratio in Group-A was 0-4, Group-B was 4.1-8 and for Group-C it was 8.1-12. Patients were evaluated for hospital admissions, need for mechanical ventilation and rate of mortality.
Results: Out of 150 patients, Group-A had 4 (8%) hospital admissions and 1 (2%) mortality, Group-B 15 (30%) had hospital admissions, and 5(10%) mortality and Group-C had 30(60%) hospital admissions and 10(20%) had mortality. Higher Neutrophil to Lymphocyte ratio is a marker for severity and poor outcomes.
Conclusion: Higher NLR was linked to disease severity and associated poor outcomes in COPD exacerbators. As a result, the NLR's utility in COPD patients should be investigated further in clinical settings in the future. If a COPD exacerbation has an NLR of 3.5-4.0, the patient may be considered eligible for outpatient follow-up without hospitalization. If the NLR is 7.5-8.0, we propose ward hospitalization; if the NLR is 11.0-12, we recommend ICU admissions.

Keywords: Lymphocytes, Neutrophils, Pulmonary disease.

How to Cite This Article: *Qureshi MM, Ashraf MN, Mariam S, Kazmi SMH, Habib MF, Ali W. Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease Exacerbators presenting to Emergency: A Marker of Disease Severity and Poor Outcomes. Pak Armed Forces Med J 2025; 75(Suppl-7): S1127-S1130. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-7.10784*

INTRODUCTION

Chronic Obstructive Pulmonary Disease is characterized by an increased chronic inflammatory response in the airways, which causes a persistent obstruction in airflow.[1] The COPD phenotype has long been thought to be linked to systemic inflammation; nevertheless, systemic inflammatory markers seem to have a role in the variability of COPD.[2] Exacerbation is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 as an immediate worsening of respiratory symptoms requiring further therapy, with severe instances requiring hospitalization or visits to the emergency room.[3] The frequency and severity of exacerbations in chronic obstructive pulmonary disease (COPD) are linked to decreased quality of life.[1-3] Exacerbations in chronic obstructive pulmonary disease (COPD) are thought to be caused by bacterial colonization as opposed to viral infection.[4] Chronic airway inflammation and the development of COPD may be aided by bacterial colonization or by exacerbations brought on by the colonization on a periodic and episodic basis.[5] Patients with severe Acute Exacerbations of Chronic Obstructive Pulmonary Diseases experience severe inflammatory eruption and gas trapping, resulting in abrupt respiratory failure and increased mortality risk.[6] Patients who have had two or more exacerbations in the last year are classified as having the 'frequent exacerbator phenotype'.[7] There are many different factors that combine to cause inflammation. Cells of the immune system, such as neutrophils and lymphocytes, that may cause long-term tissue damage if the timing of their intended destruction and aid to healing is off.[8] Neutrophils, the most common leukocytes in circulation, take involvement in a variety of

Correspondence: Dr Muhammad Mahad Qureshi, Department of Emergency Medicine, PEMH, Rawalpindi Pakistan
Received: 30 Aug 2023; revision received: 15 Feb 2024; accepted: 16 Feb 2024

immunological and inflammatory processes through phagocytosis, particle formation, cytokine release, and other mechanisms.[9] Lymphocytes have been identified as effectors and coordinators of inflammation in a variety of pathological processes.[10] Therefore, NLR is expected to be a putative biomarker reflecting the disease severity and treatment effect in COPD. Consequently, the objective of this research was to examine the relationship between NLR and clinical characteristics in patients who have recurrent exacerbations of severe COPD.

METHODOLOGY

This prospective longitudinal study was carried out on 150 patients between December 2023 to June 2023. Sample size was calculated using WHO sample size calculator taking confidence interval 95%, margin of error 5%, reported prevalence of COPD 2.1%.[11] The estimated sample size came out to be 38 patients. The sample size was increased to 150 for generalizability of results. Patients aged 40 to 80 years reporting to Emergency department in PEMH were included in the study. Non-Probability Convenience Sampling was performed. The study commenced after due approval of methodology and concept by Ethical Committee of Pakistan Emirates Military Hospitals Rawalpindi (vide A28/208(1) EC/546123). The written informed consent was taken from patients and from next of kin in cases where the patients were unable to give consent.

Inclusion Criteria: All individuals with previously diagnosed COPD on spirometry or clinically labeled as COPD by GP or pulmonology clinic, if the patient was >40 years old, and/or smoked >10 packs per year, and/or had been exposed to wood burning smoke were included in the study.

Exclusion Criteria: patients presenting with severe structural lung illness, such as tuberculosis, any active inflammatory disease other than COPD; and having any infectious, inflammatory, or malignant condition, patients with a history of antibiotic treatment in the past 10 days, usage of systemic steroids containing more than 20 mg of prednisolone per day in the previous two months were excluded.

On enrollment, complete medical and smoking history, as well as information about current pharmacologic treatments, were acquired. Baseline data was collected related to demographic characteristics, past medical history and comorbidities. Blood samples were taken from participants and total and differential leucocyte counts; absolute eosinophil and neutrophil levels were determined. Neutrophil-lymphocyte ratio was determined by dividing the neutrophil count by the lymphocyte count. Admissions were made on the basis of following local criteria:(1) those people who after optimal treatment as per GINA guidelines[12] didn't adequately respond to treatment and required further ongoing treatment, (2) had type 1 or 2 respiratory failure, (3) had poor social support and multiple co-morbidities. Admission to the following In-Hospital units were made on the following basis: (1) High Dependency Unit (HDU) – for those requiring regular nebulization and oxygen support, (2) Acute Medical Unit (AMU) – for those requiring Non-Invasive Ventilation (NIV), (3) Intensive Care Unit (ICU) – for those requiring Mechanical Ventilation at any time during their hospital stay. Discharge from emergency department, need for mechanical ventilation and mortality rates were measured. Data was recorded, entered and analyzed in Statistical Package for Social Sciences version 26.0. For quantitative data, Mean±SD and for qualitative data frequency and percentage were calculated. Chi square test was applied and *p*-value (p<0.0.5) was considered statistically significant.

RESULTS

This prospective study was carried out on 150 individuals out of which 105(70%) were male and 45(30%) were females. Furthermore, respondents were examined for smoking history and previous comorbidities. Out of total 150, 101(67.3%) were smokers and 49(32.6%) were nonsmokers. 80(53.3%) had previous multiple comorbidities like hypertension, diabetes. Comparison of Participant Characteristics in Groups with Neutrophils to Lymphocyte Ratio shown in Table-I.

Table-I: Comparison of Participant Characteristics in Groups with Neutrophils to Lymphocyte Ratio (n=150)

Variable(s)	NLR Value 0-4 (50) Group-A	NLR Value 4.1-8 (50) Group-B	NLR Value 8.1-12 (50) Group-C
Smokers	21(42%)	33(66%)	47(94%)
Non Smokers	29(58%)	17(34%)	3(6%)
No of respondents with exacerbation in last 2 years	9(18%)	16(32%)	29(58%)
Mechanical Ventilation Required	6(12%)	12(24%)	26(52%)
Admission required in high Dependence units	4(8%)	15(30%)	30(60%)
Mortality	1(2%)	8(16%)	10(20%)

NLR: Neutrophils to Lymphocyte Ratio

Results showed that Group-C with high NLR ratio had mean age of 74.31+4.9 and 60% of the

respondents required hospital admission in high dependence units and 20% had deaths in the hospitals. Table-II depicts that greater NLR is associated with greater mortality.

Table-II: Association of NLR with Mortality

Parameters	Study Groups		*p*-value
	Group-A NLR (0-4) (n=50)	Group-C NLR (8.1-12) (n=50)	
Hospitals Required In High dependency Ratio	4(8%)	30(60%)	<0.05
Mortality	1(2%)	10(20%)	<0.05

NLR: Neutrophils to Lymphocyte Ratio

For hospitals admissions required in high dependency units and mortality rates chi square test was applied between groups. Group-A NLR vs Group-C NLR and *p*-value ($p<0.05$). The highly significant results here proved that Higher NLR is a marker for severity and poor outcomes.

DISCUSSIONS

The present study found male predominance in COPD patients of 3:1, which was in accordance with a study carried out by Likhita Gutta *et al.,* where prevalence of COPD in males was found to be greater.[13] This study confirmed that higher NLR is a significant indicator of disease severity and exacerbations in COPD patients.

The results of our study are comparable with a study carried out by Karan Sharma *et al.,*[14] and Bulent Bilir *et al.,*[15] in which both the researchers found that NLR value of 3.5 or greater is a simple biomarker of inflammation that can be used to predict COPD exacerbation in patients. Present research confirmed that higher NLR is positively associated with high smoking index the results were in accordance with a study carried out by El-Gazzar *et al.,* where they found that higher NLR and Platelet to Lymphocyte Ratio (PLR) had a substantial positive relationship with smoking index, COPD stage, and dyspnea severity.[16]

Our study results show that higher NLR value >4 is associated with greater hospital admissions, this result is in agreement with a study carried out by Lee *et al.,*[17] in which they found that NLR ranges >2.8 is associated with more hospital admissions. Aksoy *et al.,* also mention in their study that the higher NLR values in their setup were associated with greater hospital admission.[18] The slight difference between NLR might be due to greater dependency of their population on hospitals, lower threshold for admissions and their small sample size. NLR is a quick, simple, and low-cost approach derived from regular complete blood count testing. Similar studies by Donaldson *et al.,*[19] Catuadella *et al.,*[20] and Issac *et al.,*[21] show NLR to be a reliable predictor of clinical outcome and severity in COPD and inflammatory illnesses. Our study results show that higher NLR is associated with greater mortality rate as NLR range 8.1 or above had higher mortality rate of 20% and is seen to be in favor of study conducted by Sorenson *et al.,* where higher NLR value is associated with greater mortality.[22]

LIMITATION OF STUDY

Small sample size, observational nature, exclusion of patients with normal results, no control group, no correlation with risk factors were studied, exclusion of frequency of exacerbations. The present results cannot be implemented on younger age than 40 years.

CONCLUSION

NLR is linked to COPD severity and exacerbations. Similarly, NLR readings in conjunction with physical findings may be relevant in determining which specific unit the patient should be admitted to. If a COPD exacerbation has an NLR of 3.5-4.0, the patient may be considered eligible for outpatient follow-up without hospitalization. If the NLR is 7.5-8.0, we propose ward HDU / AMU hospitalization; if the NLR is 11.0-12, we recommend ICU admissions.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MMQ & MNA: Data acquisition, data analysis, critical review, approval of the final version to be published.

SM & SMHK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MFH & WA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-365. https://doi.org/10.1164/rccm.201204-0596PP
2. Agusti A, Calverley P, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010; 11(1): 1-4. https://doi.org/10.1186/1465-9921-11-122

3. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010; 182(5): 598-604. https://doi.org/10.1164/rccm.200912-1843CC
4. Global Initiative for Chronic Obstructive Lung Disease Global strategy for diagnosis, management, and prevention of COPD. [Internet] . Available at: https://goldcopd.org/ [Accessed on November 27, 2023]
5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007; 370: 765-773. https://doi.org/10.1016/S0140-6736(07)61380-4
6. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. New Eng J Med 2008; 359(22): 2355-2365. https://doi.org/10.1056/nejmra0800353
7. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, et al. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017; 195(3): 324-330. https://doi.org/10.1164/rccm.201605-1014OC
8. Le Rouzic O, Roche N, Cortot AB, Tillie-Leblond I, Masure F, Perez T, et al. Defining the "frequent exacerbator" phenotype in COPD: a hypothesis-free approach. Chest 2018; 153(5): 1106-1115. https://doi.org/10.1016/j.chest.2017.10.009
9. Nathan C. Points of control in inflammation. Nature. 2002; 420(6917): 846-852. https://doi.org/10.1038/nature01320
10. Németh T, Sperandio M, Mócsai A. Neutrophils as emerging therapeutic targets. Nat Rev Drug Discov 2020; 19(4): 253-275. https://doi.org/10.1038/s41573-019-0054-z
11. Khan MA, Khan MA, Walley JD, Khan N, Sheikh FI, Ali S, et al. Feasibility of delivering integrated COPD-asthma care at primary and secondary level public healthcare facilities in Pakistan: a process evaluation. BJGP open 2019; 3(1): bjgpopen18X101632. https://doi.org/10.3399/bjgpopen18X101632
12. Dubin S, Patak P, Jung D. Update on Asthma Management Guidelines. Mo Med 2024; 121(5): 364-367.
13. Gutta L,Ahmed T. NLR and PLR Ratios-Accessible and Affordable Predictors of Disease Severity in COPD. J Assoc Physicians Ind 2022; 70(4): 11-12. https://doi.org/ 10.1038/s41598-022-20385-3
14. Sharma K, Garg K, Joshi Jl, Chopra V, Kundal Rk. Neutrophil-Lymphocyte Ratio as a Predictor of COPD Exacerbations: A Cross-sectional Study. J Clin Diagnostic Res 2023; 17(1); OC18 - OC21. https://doi.org/10.7860/JCDR/2023/59293.17337
15. Bilir B, Altintaş n, Aydin M, Oran M, Ozsu S, Tutar U. The predictive role of neutrophil to lymphocyte ratio in chronic obstructive pulmonary disease. European J Gen Med 2016; 13(2): 105-110. https://doi.org/10.15197/ejgm.1554
16. El-Gazzar AG, Kamel MH, Elbahnasy OK, El-Naggar ME. Prognostic value of platelet and neutrophil to lymphocyte ratio in COPD patients. Expert Rev Respir Med 2020; 14(1): 111-116. https://doi.org/10.1080/17476348.2019.1675517
17. Lee SJ, Lee HR, Lee TW, Ju S, Lim S, Go SI, et al. Usefulness of neutrophil to lymphocyte ratio in patients with chronic obstructive pulmonary disease: a prospective observational study. Korean J Int Med 2016; 31(5): 891. https://doi.org/doi: 10.3904/kjim.2015.084
18. Aksoy E, Karakurt Z, Gungor S, Ocakli B, Ozmen İ, Yildirim E, et al. Neutrophil to lymphocyte ratio is a better indicator of COPD exacerbation severity in neutrophilic endotypes than eosinophilic endotypes. International J chronic obstructive pulmonary dis 2018: 2721-2730. https://doi.org/10.2147/COPD.S170353
19. Donaldson GC, Seemungal TA, Patel IS, Bhowmik A, Wilkinson TM, Hurst JR, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest 2005; 128(4): 1995-2004. https://doi.org/10.1378/chest.128.4.1995
20. Cataudella E, Giraffa CM, Di Marca S, Pulvirenti A, Alaimo S, Pisano M, et al. Neutrophil-to-lymphocyte ratio: an emerging marker predicting prognosis in elderly adults with community-acquired pneumonia. J Am Geriatrics Society 2017; 65(8): 1796-1801. https://doi.org/10.1111/jgs.14894
21. Isaac V, Wu CY, Huang CT, Baune BT, Tseng CL, McLachlan CS. Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. Med 2016; 95(23): e3832. https://doi.org/:10.1097/MD.0000000000000383
22. Sørensen AK, Holmgaard DB, Mygind LH, Johansen J. Neutrophil-to-lymphocyte ratio, calprotectin and YKL-40 in patients with chronic obstructive pulmonary disease: correlations and 5-year mortality–a cohort study. J Inflammation 2015; 12(1): 1-2. https://doi.org/ 10.1186/s12950-015-0064-5

.....