## General Medicine

# NEUTROPHIL-LYMPHOCYTE RATIO AS A MARKER OF DISEASE SEVERITY AND EXACERBATION IN COPD

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**ABSTRACT**  **CONTEXT:**Since the burden of COPD is increasing day by day and is a leading cause of mortality ,it is important to have a prognostic marker for COPD. The well known prognostic marker for COPD is the BODE score,which includes 1)BMI  2)Degree Of Obstruction 3)Dyspnoea Scale 4)Exercise Capacity. Since the calculation Of BODE score is cumbersome and is not possible in sickpatients, it is important to have a simple prognostic marker like Neutrophil Lymphocyte Ratio(NLR) which can be easily obtained from a routine complete blood count which correlates well with that of BODE score

**AIM OF THE STUDY:** To assess whether Neutrophil-to-Lymphocyte ratio can be used to assess the severity of disease by comparing it with BODE score in COPD.
-To assess whether the Neutrophil Lymphocyte ratio is higher in COPD exacerbation compared to patients with stable COPD.

**SETTINGS AND DESIGN:** Analytical Cross-sectional study

**MATERIALS AND METHODS:**The study is to be conducted among 80 patients which includes 30 patients who attend the emergency department of Gov.Rajaji Hospital,Madurai in a state of COPD Acute exacerbation and 50 Stable COPD patients who attend  the OPD for followup.

**STATISTICAL ANALYSIS:**Data analysis was done with statistical software SPSS.16 software and Sigma Stat 3.5 version . Using this software, mean, standard deviation and p-value were calculated through One way ANOVA, Chi-square test .P- value of < 0.05 was taken as significant. Pearson correlation coefficient was used to find correlation between 2 variables.

**RESULTS:** COPD is more prevalent among smokers and male sex.  Low BMI is a risk factor for severe disease. NLR correlated with the severity of air flow obstruction . NLR has a positive correlation with mMRC  scale. NLR correlated inversely  with  6-minute walk distance.Thus,NLR  correlated inversely with BMI,FEV1%,6-minute walk distance  and  has a positive correlation with mMRC scale. NLR correlated with the disease severity as it has positive  correlation with BODE score. NLR was significantly higher in COPD exacerbation compared to  patients with stable COPD

**CONCLUSIONS:** NLR correlates well with the disease severity in stable COPD as compared to BODE score. So, it should be used as a routine prognostic marker of mortality in all patients with COPD .  NLR can be used as a marker of COPD exacerbations.

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a avoidable and treatable common disease characterized by progressive and permanent airflow limitation associated with increased chronic inflammatory response of the lungs and airways against injurious gases and particles.One of the characteristic features of COPD is acute exacerbations,which usually are associated with increased inflammation due to infections and/or environmental factors. It is possible that bacterial colonization itself, or recurring and intermittent exacerbation caused by the colonization, may contribute to chronic airway inflammation and the progression of COPD .

Inflammation is a complex set of relations among various immune-related cells, including neutrophils and lymphocytes,which can lead to persistent tissue damage if targeted destruction and assist repair are not properly phased. Leucocyte count and its subtypes are well-known markers of inflammation.Since the physiological response of the leucocytes in circulation against stress precipitates an increase in neutrophil count and decrease in the lymphocyte count, the ratio of these two sub-groups to one another is engaged in the intensive care practice.In various recent studies, neutrophil-to-lymphocyte ratio (NLR) has been evaluated for its probable role in the inflammation periods of chronic diseases such as pancreatitis,acute coronary syndrome etc.

It has been established in previous studies that various inflammatory markers like C-reactive protein (CRP), fibrinogen and leucocyte count increase in stable patients of COPD as well as in exacerbation and that this increase is associated with the negative results of the disease. Unlike other inflammatory biomarkers e.g., ESR and CRP,the Neutrophil–lymphocyte ratio (NLR) is derived from routine complete blood count (CBC) tests. It does not need a special request. It is a rapid, easy and cost-effective method.

The current study is undertaken to analyse the Neutrophil to lymphocyte ratio(NLR) in COPD exacerbation and stable COPD patients.Also to check whether the NLR could reflect the disease severity in such patients as compared with BODE score in COPD.

## MATERIALS AND METHODS

**Study Population:** The study is to be conducted among 80 patients which includes 30 patients who attend the emergency department of Gov.Rajaji Hospital,Madurai in a state of COPD Acute exacerbation and 50 Stable COPD patients who attend the OPD for followup. Criteria for COPD Exacerbation- any patient with a worsening of more than two respiratory symptoms(dyspnoea,sputum,cough or wheeze) for two or more consecutive days can be considered as exacerbation. Criteria for stable COPD-no symptoms of exacerbation and no use of systemic corticosteroids or antibiotics for the preceding 8 weeks.
Inclusion Criteria:

All patients with a confirmed diagnosis of COPD diagnosed with pulmonary function test according to GOLD(Global Initiative for Chronic Obstructive Lung Disease) criteria

## EXCLUSION CRITERIA:

Bronchial asthma ,bronchiectasis ,or bullous lung disease Active tuberculosis or any history of pulmonary fibrosis,  Anytumour, hepatitis, thyroiddiseases ,autoimmune diseases, or any other acute infections,  Dementia Receiving systemic corticosteroids, antibiotics ,or immunosuppressive treatment, Not free from an Exacerbation for atleast preceeding 8 weeks Withdrawal of consent.

**ETHICAL COMMITTEE APPROVAL: OBTAINED.**
**STUDY PROTOCOL:**
A previously designed proforma will be used to collect the demographic and clinical details of the patients. Detailed history

pertaining to present illness as well as a thorough history regarding other disease conditions were obtained. All patients are interviewed and clinically examined. Informed consent will be obtained from all subjects for clinical examination. Patient confidentiality will be maintained.

Patients with acute exacerbation of COPD brought to the Medicine casualty and also stable COPD patients attending the Thoracic Medicine OPD of Gov.Rajaji Hospital,Madurai. Informed consent was be taken A detailed history including duration of illness,smoking history,packyears and any past medical history was taken. Degree of dyspnoea was assessed using Modified Medical Research Council(MMRC) dyspnoea scale . Pulmonary function tests were done including FEV1/FVC and Post- bronchodilator FEV1 Peripheral blood samples were collected from all patients within 24hours of admission which includes total count,differential count of neutrophils and lymphocytes. Neutrophil-to-lymphocyte ratio was calculated by dividing absolute neutrophil count by absolute lymphocyte count

## STATISTICAL ANALYSIS
The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with statistical software SPSS.16 software and Sigma Stat 3.5 version . Using this software, mean, standard deviation and p-value were calculated through One way ANOVA, Chi-square test .P- value of < 0.05 was taken as significant. Pearson correlation coefficient was used to find correlation between 2 variables.

## RESULTS :
## AGE DISTRIBUTION IN COPD:

In our study including 80 cases

| Age | No. of Cases | Percentage |
|---|---|---|
| 41-50 | 12 | 15 |
| 51-60 | 20 | 25 |
| 61-70 | 33 | 41.2 |
| 71-80 | 11 | 13.8 |
| >80 | 4 | 5 |

## SEX DISTRIBUTION

| Sex | No. of Cases | Percentage |
|---|---|---|
| Male | 68 | 85 |
| Female | 12 | 15 |

## SMOKING AND COPD
In our study 68 cases (85%) out of 80 cases were smokers.

| Smokers (Pack years) | No. of Cases | Percentage |
|---|---|---|
| <20 | 11 | 16.2 |
| 20-29 | 22 | 32.4 |
| 30-39 | 17 | 25 |
| 40-49 | 12 | 17.6 |
| >50 | 6 | 8.8 |

## BMI AND COPD

| BMI | No. of Cases | Percentage |
|---|---|---|
| <18 | 18 | 22.5 |
| 18-18.9 | 19 | 23.8 |
| 19-19.9 | 21 | 26.2 |
| 20-20.9 | 10 | 12.5 |
| 21-21.9 | 8 | 10 |
| >22 | 4 | 5 |

## RELATION BETWEEN BMI AND NLR
As NLR increases,mean BMI decreases. NLR is associated with disease severity. Hence,it can be inferred that lower BMI is associated with severe disease and poor prognosis.

| NLR groups | Mean BMI |
|---|---|
| 0 to 2.5 | 20.62 |
| 2.6 to 5 | 19.21 |
| 5.1 to 7.5 | 18.43 |
| 7.6 to 10 | 17.8 |

## FEV1 % AND COPD

| FEV1 % | No.of cases | Percentage |
|---|---|---|
| <30 | 13 | 16.2 |
| 30-49 | 33 | 41.2 |
| 50-79 | 22 | 27.5 |
| >80 | 12 | 15 |

## RELATION BETWEEN FEV1% AND NLR
Shows significant p-value(0.001) using ANOVA test. That is,FEV1% decreases ,NLR increases Ie.MORE severe the airflow obstruction(as evidenced by decreasing FEV1), Higher the NLR

| NLR | FEV1%(MEAN) |
|---|---|
| 0 to 2.5 | 73 |
| 2.6 to 5.0 | 51.9 |
| 5.1 to 7.5 | 38.4 |
| 7.6 to 10 | 27 |

## MODIFIED MEDICAL RESEARCH COUNCIL SCALE(MMRC) AND COPD

| mMRC scale | No. of Cases | Percentage |
|---|---|---|
| 0 | 2 | 2.5 |
| 1 | 3 | 10 |
| 2 | 30 | 37.5 |
| 3 | 21 | 26.2 |
| 4 | 19 | 23.8 |

## CORRELATION BETWEEN NLR AND MMRC SCALE
The correlation coefficient between NLR and mMRC scale is 0.825. Hence,there is a positive correlation between NLR and mMRC scale. So,as the mMRC grade increases,NLR also increases.

| Correlation between NL ratio grp and MMrC grade | | | R value | |
|---|---|---|---|---|
| Spearman's rho | NL_ratio_grp and MMrC grade | Correlation Coefficient | 0.825** | Positively correlated |
| | | p value | .004 | |

## RELATION BETWEEN NLR AND 6-MINUTE WALK DISTANCE

| NLR | 6-minute walk distance |
|---|---|
| 0 to 2.5 | 413.3 |
| 2.6 to 5 | 317.6 |
| 5.1 to 7.5 | 254 |
| 7.6 to 10 | 133.3 |

Shows significant p value(0.001) by anova test

AS NLR increases,the mean 6-minute walking distance decreases. NLR is inversely correlated with 6-minute walk distance.

## BODE SCORE



Distribution of BODE score among Stable COPD group
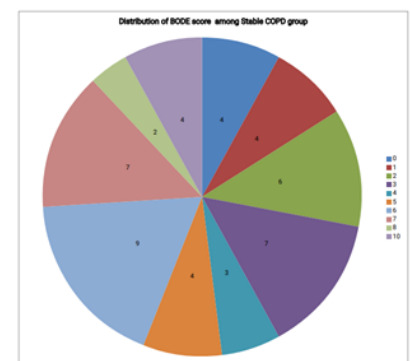
## NEUTROPHIL LYMPHOCYTE RATIO(NLR)

| | | NL_ratio_grp | | | | |
|---|---|---|---|---|---|---|
| | | 0 to 2.5 | 2.6 to 5 | 5.1 to 7.5 | 7.6 to 10 | P value |
| Stable COPD | frequency (n) | 15 | 17 | 15 | 3 | |
| | % within | 30.0% | 34.0% | 30.0% | 6.0% | 0.01 |
| Exacerbated COPD | frequency (n) | 2 | 10 | 15 | 3 | |
| | % within | 6.7% | 33.3% | 50.0% | 10.0% | |
| Total | frequency (n) | 17 | 27 | 30 | 6 | |
| | % within | 21.2% | 33.8% | 37.5% | 7.5% | |

## COMPARISON OF NLR BETWEEN STABLE COPD AND COPD EXACERBATION GROUP
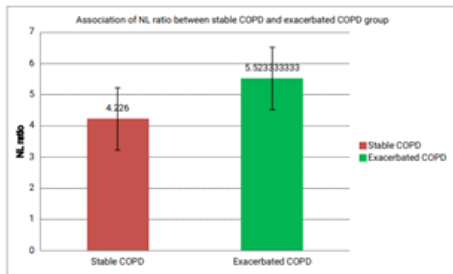


Comparison of NLR between the stable and exacerbated COPD was done using the unpaired t-test and was found to be statistically significant (p value-0.008) It is found that NLR is higher among the COPD Exacerbation group as compared to stable COPD. Hence, it can be inferred that NLR can be used as a marker of COPD exacerbation.

## NLR AND BODE

| | | BODE score | | | | | P value |
|---|---|---|---|---|---|---|---|
| | NLR | 0 to 2 | 3 to 5 | 6 to 8 | 9 to 10 | Total | |
| 0 to 2.5 | Count | 13 | 2 | 0 | 0 | 15 | |
| | % within bode | 92.9% | 14.3% | .0% | .0% | 30.0% | |
| 2.6 to 5 | Count | 1 | 11 | 5 | 0 | 17 | |
| | % within bode | 7.1% | 78.6% | 27.8% | .0% | 34.0% | |
| 5.1 to 7.5 | Count | 0 | 1 | 13 | 1 | 15 | 0.0001 |
| | % within bode | .0% | 7.1% | 72.2% | 25.0% | 30.0% | |
| 7.6 to 10 | Count | 0 | 0 | 0 | 3 | 3 | |
| | % within bode | .0% | .0% | .0% | 75.0% | 6.0% | |
| Total | Count | 14 | 14 | 18 | 4 | 50 | |
| | % within bode | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | |

* Shows significant p value chi square test

As NLR increases, BODE score increases There is positive correlation between BODE and NLR Correlation coefficient +0.916 Hence, NLR can be used to assess the disease severity as it correlates with BODE score.

## DISCUSSION

In our study,all the cases are aged above 40 years.Maximum number of cases(33) fell between 61-70 years.The findings of our study are similar to our earlier knowledge since COPD is a disease affecting elderly persons.

In our study,85% of patients were males and 15% were females.The higher prevalence in males is probably due to the higher prevalence of smoking in males. All the males in our study are smokers and all the females are nonsmokers.Cigarette smoking is a major etiological risk factor for COPD.In our study,it is proved beyond doubt that there is a significant association between smoking and COPD.

Our study shows that a low BMI is associated with a high NLR and severe disease.Hallin et al[10] in 2006 reported that low BMI and weight change ere related to a poor prognosis in COPD.Pouw et al[11] in 2000 reported that low BMI is a risk factor for unplanned readmission.Hence,our results are in accord with the previous studies that further efforts are needed to improve the nutritional status in patients with COPD.

In our study,majority of patients[41.2%] came under GOLD stage 3.As FEV1% decreases,NLR increases.ie.as the severity of airflow obstruction increases,NLR increases.Thus,NLR indirectly reflects the extent of airflow obstruction.A possible underlying mechanism is that activated neutrophils cause tissue destruction in lungs by releasing oxygen radicals and proteolytic enzymes which results in emphysema.Emphysematous changes may lead to small airway obstruction.Yasar et al[ 22] in 2015 have detected a negative correlation between NLR and FEV1%.Our study has also yielded the same.

In our study, majority (37.5%) had a mMRC dyspnoea scale of 2.We obtained a positive correlation (0.825) between NLR and mMRC. The relation between NLR and 6-minute walk distance as also assessed.As NLR increases,the 6-minute walk distance reduced.Thus,NLR and 6-minute walk distance are inversely correlated.Ryuko et al in 2016 has also yielded similar results. The relation between NLR and BODE scores were assessed.There is a positive correlation between NLR and BODE score with a p-value of 0.0001 and correlation coefficient of 0.916.

Celli et al [24] in 2004 constructed the BODE score to predict the risk of death among patients with COPD.Seung et al in 2016 has demonstrated the association between NLR and BODE score as well as with individual components of BODE.They showed significant correlation between NLR and BODE score,mMRC and 6 minute walk distance whereas no correlation was identified between NLR and BMI or FEV1.But our study contradicts their study in that NLR have been correlated well with BODE score as well as with mMRC,6-minute walk distance,BMI and FEV1%.

Another important observation was that NLR was higher among the COPD exacerbation group as compared to the stable COPD group with a p value of 0.008.Hence,it can be inferred that NLR can be used as a marker of COPD exacerbation. Thus,NLR can be used as a prognostic indicator and determinant of severity of COPD is well proved statistically in our study.

## CONCLUSION
* NLR was significantly higher in COPD exacerbation compared to patients with stable COPD
* NLR correlated with the disease severity as it has positive correlation with BODE score
* COPD is more prevalent among smokers and male sex
* Low BMI is a risk factor for severe disease
* NLR correlated with the severity of airflow obstruction
* NLR has a positive correlation with mMRC scale
* NLR correlated inversely with 6-minutre walk distance
* Thus,NLR correlated inversely with BMI,FEV1%,6-minute walk distance and has a positive correlation with mMRC scale.
* So,NLR has got significant correlation with BODE score as well as all the individual parameters in BODE score.
* Since NLR correlates well with the disease severity in COPD,it should be used as a routine predictive marker of mortality in all patients with COPD since it is simple,cost-effective and can be obtained from a routine complete blood count in comparison to calculating the BODE score which is cumbersome.

## LIMITATIONS
1. Relatively small sample size 2. BODE score could only be assessed in the stable COPD group 3. It is a cross-sectional study,hence control groups could not be involved

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