

SIGNIFICANCE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Background: To Evaluate the clinical significance of Neutrophil- to - Lymphocyte Ratio (NLR) in Chronic Obstructive Pulmonary Disease patients presenting with Acute exacerbations. **Materials and Methods:** It is a retrospective study of 128 patients diagnosed with acute exacerbation of COPD (AECOPD) and presented to the casualty at Mamata Academy of Medical Sciences, Bachupally, Hyderabad from December 2022 to May 2023. All patients aged more than 40 years with a previous diagnosis of COPD based on Spirometry who came with acute exacerbations were included in our current study. The Ratio of Neutrophils to Lymphocytes of these patients were calculated using their total leucocyte count which were obtained by complete blood picture at laboratory examination. **Result:** In this study out of 128 patients 106 improved, 15 died and 7 were transferred out. The mean NLR of patients who required ICU admission was 8.5 compared to patient admitted in general ward which was 4.58. The area under curve (AUC) was 0.67, with p value of 0.002 which was significant. Mean NLR of patients was highest among the patients who required intubation (23.26) followed by the ones who required non-invasive ventilation (7.88). The AUC was 0.77 with significant p value of <0.00001. Among the patients who were discharged mean NLR was 6.17 while the NLR was 19.7 among the patients who did not survive. The area under the curve is 0.86, with p value of <0.00001 suggesting high NLR had worst outcome. **Conclusion:** In the current study we concluded that higher NLR is significantly associated with requirement of ICU admission (AUC=0.678, p=0.002) and also need of invasive ventilation (AUC=0.77, p=<0.00001) in cases of AECOPD. Also high NLR values in AECOPD patients was associated with increased deaths.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous group of lung diseases characterized by symptoms like dyspnea, cough, sputum production and/or exacerbations which are chronic and is due to abnormalities of the airways and/or alveoli that cause persistent, often progressive, irreversible airway obstruction.^[1] Emphysema and Chronic Bronchitis are the two major diseases included in COPD. Bronchiolitis (small airways) are also considered to be a part of this disease spectrum. COPD patients frequently develop multi systemic

manifestations like muscle wasting and cachexia. They often have comorbidities like heart failure, ischaemic heart disease, osteoporosis, lung malignancies and depression. COPD is one of the leading causes of morbidity and mortality worldwide. Its predicted that by 2030 it will be third most common cause of mortality in the world. About 90 percent of COPD deaths take place in poor socioeconomically backward and developing countries.^[2] The incidence of COPD is most common due to use of tobacco smoke, though indoor and outdoorair pollution, Occupation and burning of

wood and other biomassfuels also contribute significantly.^[3]

An exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in <14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways.^[1] Patients are managed with inhaled bronchodilators and steroids with antibiotics but majority of them require hospitalization. Patients with type 2 respiratory failure will require intensive care management with non invasive ventilation and intravenous antibiotics. Assessing the patient clinically according to severity is very important as it will provide prompt and appropriate treatment to the patient. Timely intervention will provide proper treatment reducing hospital stay and will have socioeconomic benefit. At present, we don't have any standard objective for assessing AECOPD severity. The severity of the AECOPD is assessed based on patients history and physical examination along with chest radiography, blood gas and commonly used of biomarkers like (CRP, Procalcitonin). Thus need for a single biomarker, which is rapid and affordable is the need of the hour.

Neutrophil to lymphocyte ratio (NLR)in blood is considered to be a valuable biomarker produced during various systemic inflammatory conditions. NLR is calculated using total neutrophils upon the total lymphocytes in the blood.^[4]

NLR = Relative % Neutrophils

Relative % Lymphocytes

Interpretation of NLR:

- Normal range of NLR is about 1-3
- NLR between 6 to 9 it indicates mild stress
- Critical patients can have an NLR of 9 or above (occasionally reaching values close to 100).^[4]

In a number of recent studies, the NLR value has been found to be markedly raised in inflammatory phases of chronic illnesses. AECOPD is an inflammatory condition where an elevated NLR could be considered as a predictive biomarker for infection. In a recent study compared to standard markers like C-reactive protein (CRP), Total leucocyte count (TLC) count and neutrophil counts, NLR value was found to be a better marker of infection.^[5] Previous datas on community acquired pneumonia (CAP) showed the NLR values to be a good predictor in assessing the severity of CAP than the routine infection markers like TLC, neutrophils and CRP values.^[6,7]

H. El Sayed Z et.al (2019) demonstrated the marked variations in the average value of NLR between COPD patients according to severity. According to the studies, Neutrophils were seen to gradually increase from mild to very severe COPD patients and the lymphocytes were in decreasing trend in mild to very severe COPD groups.^[8]

Lu et.al (2022) in their article stated that recurrent exacerbators during severe AECOPD have a higher

NLR value and a higher percentage of poorer outcomes. According to A.M.Yousef et.al (2016) for the assessment of inflammation in COPD patients, NLR can be employed as a novel inflammatory marker and is a reliable indicator of AECOPD.^[8] Our study looked into the predictive NLR value in AECOPD patients pertaining to their treatment modalities and outcomes.

MATERIALS AND METHODS

It is a retrospective study of 128 patients with a diagnosis of AECOPD in Mamata Academy of Medical Sciences, Bachupally, Hyderabad from December 2022 to May 2023. The institutional Ethics Committee approved this study. All patients aged more than 40 years with a previous confirmed diagnosis of COPD based on Spirometry who came with acute exacerbations were included in our study. All COPD patients who have any illness affecting their Neutrophil and/or Lymphocyte count in the blood like as Bronchiectasis, Tuberculosis, Malignancy, hematological conditions or any inflammatory diseases were excluded from the study. Patients using drugs like granulocyte colony-stimulating factor and patients who had granulocytic deficiency caused by non-inflammatory factors were excluded from our study. The demographics and clinical characteristics were collected and entered in Data information sheet.

Statistical analysis: The data was entered in Microsoft (MS Excel)2010 version. Analysis of this data was done using MS Excel 2010 and Epi Info 7.2.0. Descriptive statistics were depicted as frequencies, percentages and means, while the inferential statistics like t test and ANOVA were done to test the significance. p value of <0.05 was considered to be statistically significant.

RESULTS

The study was conducted in a total of 128 patients diagnosed with AECOPD of which 121 (94.5%) were males and 7 were females (5.47). Majority of patients were belonging to the age group of 60-69 (Mean=45) followed by 70-79 (Mean=34). Smoking was risk factor in a whopping number of 108 patients, while only 20 patients were non-smokers. [Table 1]

The occupancy rate in ICU was analysed using the frequency of requirement for invasive mechanical ventilation and treatment outcome on which the ROC curve analysis was done. In our study population, the mean NLR of patients who required ICU admission was significantly higher than the patients who were managed in the general ward (8.5 & 4.58 respectively) with AUC 0.67, with p value of 0.002. [Table 3, Figure 1]

In the given study population, the mean NLR of patients was highest among the patients who required intubation (23.26) followed by the ones who required non-invasive ventilation (7.88). The ones on oxygen

supplementation had the least NLR (4.15). The mean values obtained clearly suggests that higher the NLR, higher is the requirement of Oxygen supplementation & mechanical ventilation. The AUC is 0.77 with significant p value of <0.00001. [Table 5, Figure 2] In this study out of 128 patients, 106 improved, 15 died and 7 were transferred out. [Table 6] In the given

study population higher NLR was markedly associated with adverse outcome. The average NLR of the patients who were discharged was 6.17, those who were transferred out was 8.68. The NLR was highest among the patients who did not survive (19.71). The area under the curve is 0.86, with p value of <0.00001. [Table 7, Figure 3]

Table 1: Baseline characteristics of the study population (n=128)

Variable		Frequency (n=128)	Percentage (100)
Age group	40-49 years	12	9.38
	50-59 years	29	22.66
	60-69 years	45	35.16
	70-79 years	34	26.56
	80 and above	8	6.25
Gender	Male	121	94.5
	Female	7	5.5
Smoking	Smoker	108	84.3
	Non smoker	20	15.7

AECOPD was most common among age group of 50 to 79. Above graph shows the presentation among various age groups. Study showed more male patients (121) presenting with acute exacerbation of COPD compared to female patients (7). Out of 128 included in study 108 were smokers and 20 were nonsmokers.

Table 2: Distribution according to type of admission (n=128)

Admission	Frequency	Percentage
ICU	107	83.59
Ward	21	16.41
Grand Total	128	100

Out of 128 patients 107 were admitted in ICU and 21 in wards.

Table 3: Distribution as per Type of admission and mean NLR (n=128)

Admission	Mean NLR	T test p Value
ICU	8.50 ± 8.08	0.002
Ward	4.58 ± 4.29	

Table 4: Number of patients requiring oxygen supplementation and different modes of ventilation (n=128)

Mode	Frequency	Percentage
Invasive	11	8.59
Non invasive	72	56.25
Oxygen supplementation	45	35.16
Grand Total	128	100.00

Table 5: NLR variability in patients requiring oxygen supplementation and different modes of ventilation (n=128)

Mode	Mean NLR	ANOVA p Value
Invasive	23.26±15.54	<0.00001
Non invasive	7.88 ± 4.65	
Oxygen supplementation	4.15 ± 3.12	

Table 6: Distribution according to Outcome of the study population (n=128)

Outcome	Frequency	Percentage
Death	15	11.72
Improved	106	82.81
Transferred out	7	5.47
Grand Total	128	100.00

Table 7: Relation to NLR variation & outcomes (n=128)

Outcome	Mean NLR	ANOVA p Value
Death	19.71 ± 11.34	<0.00001
Improved	6.17 ± 5.51	
Transferred out	8.68 ± 5.73	

Table 8: Showing the AUC of NLR with study parameters (n=128)

Parameter	AUC value
ICU admission	0.678 (0.54 - 0.80)
Invasive ventilation requirement	0.77 (0.61 - 0.93)
Mortality	0.86 (0.78 - 0.94)

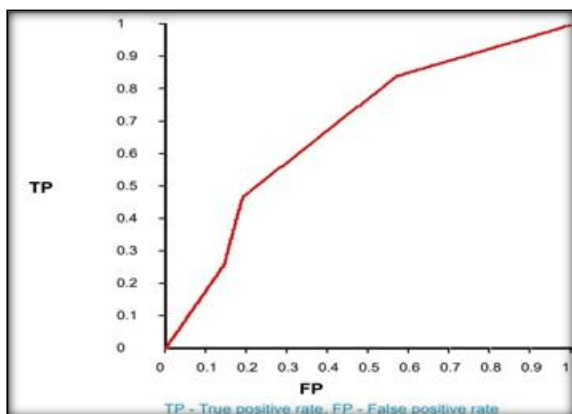


Figure 1: Figure showing the area under curve (AUC) between ICU admissions and NLR ratio

Area under the curve: 0.678 (0.548 - 0.809)

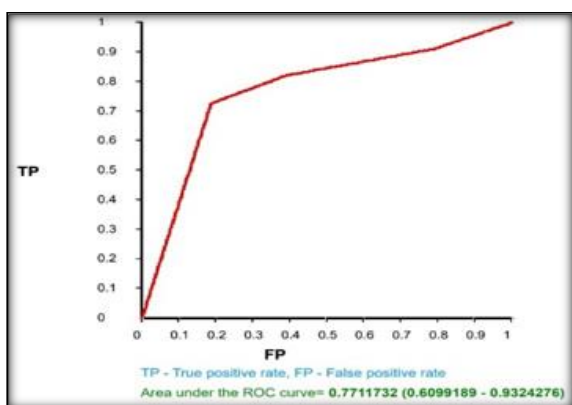


Figure 2: Figure showing the area under curve (AUC) between different modes of ventilation and NLR ratio

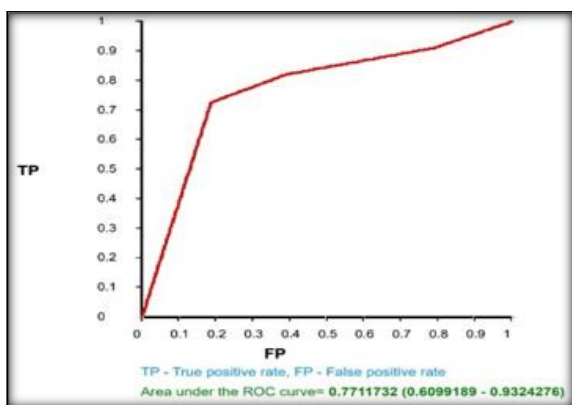


Figure 3: Showing the area under the curve (AUC) between outcomes and NLR ratio

DISCUSSION

A sudden change in the intensity of COPD symptoms like cough, expectoration and dyspnoea compared to the baseline level of symptoms is known as an acute exacerbation. Exacerbations can be caused by a number of factors. The common factors include respiratory tract infections, either viral or bacterial, eosinophil-predominant or mixed. Non-inflammatory conditions like low mean ambient temperatures, air pollution and comorbidities can also be risk factors.

Non compliance to maintenance therapy can also lead to exacerbations. The exact cause of exacerbation may not be identified in one third of the cases. About 70% of exacerbations are caused by viral infections whilst some studies suggest that bacterial infections are causes for more than 50% of exacerbations.^[9] COPD is largely irreversible and leads to progressive airflow limitations that is caused by chronic inflammation of the peripheral airways and the lung parenchyma. The inflammation typically give rise to increase in the alveolar macrophages, Neutrophils, T lymphocytes and innate lymphoid cells.^[10] Recurrent exacerbations leading to persistent expectoration, airway obstruction and a rapid decline in lung function can give rise to increase production of neutrophils in the sputum.^[11] The consequences of AECOPD includes increase symptoms (cough, dyspnoea), poor quality of life, deterioration in lung function (acute and permanent), increased health care utilization and long and short term mortality.

Seung Jun Lee et al. found that the NLR value was very high in patients with AECOPD than in stable COPD patients.^[12]

Allan Klitgaard Sørensen et al. found that low lymphocyte count is a good predictor of infection.^[13] Roser Terradas et al. reported that NLR more than 7 in patients with infection was an independent risk factor of mortality.^[14]

Research by Mahsuk Taylan et al,^[15] reported that usual inflammatory markers like (CRP, ESR and TLC) were useful in assessing exacerbations of COPD but the value of NLR was more sensitive. In present study, the NLR was markedly high in patients admitted in ICU than those in wards indicating that high NLR value suggest severe infection and requirement of intensive monitoring.

Noninvasive ventilation is the main stay in the treatment of AECOPD. It reduces hypercapnia, respiratory acidosis, dyspnoea, and mortality. Also the requirement for intubation and invasive mechanical ventilation is shortened thus reducing the hospital stay and mortality.^[16]

High NLR value was an independent predictor for the requirement of Invasive Mechanical Ventilation in patients with AECOPD. This study also concluded that patients with higher NLR values needed mechanical ventilation the most.

Ritumbhara et.al (2022), showed that AECOPD had higher NLR on the day of hospitalization compared to stable COPD patients. They also stated that patients having high NLRs upon admission had worse chance of survival.^[17]

Liu J et.al (2019) stated that an increased risk of 90-day mortality in individuals with AECOPD was indicated by the high NLR values. Hence, NLR could be a significant predictor of ICU admissions and poorer outcomes.^[18]

In our study population, out of 128 patients, 106 improved and 15 patients died. The poorer outcome was more among patients with high NLR. The average NLR of the patients who were discharged

was 6.17 and who did not survive was 19.71. The area under the curve is 0.86, with p value of <0.00001.

In an emergency while assessing the severity and outcome of AECOPD patients NLR can be helpful to the physician's. It can guide in developing a treatment plan. The NLR can be easily applied in hospitals with low resource settings because of its availability and affordability with an extensive application prospect.

CONCLUSION

Our study concluded that higher NLR ratio is significantly associated with Intensive Care Unit admission (AUC=0.678, p=0.002) along with invasive mechanical ventilation (AUC=0.77, p<0.00001) and mortality (AUC=0.86, p<0.00001). Since patients taken in this study are only limited in number, we suggest further studies for more inferences.

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