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Original Research Article

Correlation of neutrophil to lymphocyte with acute exacerbation in chronic obstructive pulmonary disease at tertiary care hospital in North West Rajasthan

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ABSTRACT

Background: Acute exacerbation of COPD (AECOPD), is one of the most common disease in patients with infections, having frequent hospitalization. The aim of this study is to evaluate the potential for NLR to be used as a biomarker of COPD exacerbation.
Materials and Methods: The hospital based case control Study is was conduct on hospitalized 100 patient with primary and final diagnosis of AECOPD and 100 patient of stable period of COPD.
Results: Socio-demographic variable in both groups were comparable. BMI was significantly lower in AECOPD patients. The mean PACK/YR in AECOPD group was 29.52±3.70 and in Stable COPD was 23.50±2.05. FEV1was significantly lower in AECOPD patients. Mean admission per year was significantly higher in AECOPD patients. Mean neutrophil count was significantly higher in AECOPD patients (11.49±2.32) as compare to stable COPD patients (6.47±2.01). Mean lymphyocyte count was significantly higher in AECOPD patients (2.07±0.05) as compare to stable COPD patients (1.71±0.07). Mean NLR was significantly higher in AECOPD patients (5.54±2.12) as compare to stable COPD patients (3.77±0.22). The difference in both groups was found statically significant. 5.00% hospital mortality in AECOPD patients. Mean neutrophil count was significantly higher in death as compare to survived patients. Mean NLR was significantly higher in death as compare to survived patients.
Conclusions: NLR is readily available (Available at PHC) and simple parameter, could also be used as a cost-effective marker of inflammation in AECOPD. We have concluded that the neutrophil lymphocyte ratio on the day of presenting the illness was significantly higher in AECOPD as compare to stable COPD. Those patients who had a high NLR during admission were associated with poor survival.

1. Introduction

Chronic obstructive pulmonary disease (COPD) a preventable and treatable disease which consists of constant expiratory limitation of the flow of air which is not fully reversible. Detection of COPD is thought in a patient coming with symptoms of cough, excessive production of sputum, or dyspnea and/ or exposure to factors which causing the disease will be present.

GOLD defines COPD – "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/ or alveolar abnormalities usually caused by significant exposure to gases or noxious particles". [1]

The global initiative for chronic obstructive lung disease (GOLD) has classified COPD in four stages depending upon the spirometric findings.

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Table 1: Classification of severity of air flow limitation in COPD as per GOLD criteria

Classification of COPD by impairment of lung function		
Stage	**Severity**	**Spirometry (postbronchodilator)**
Gold 1	Mild	FEV_1, ≥80% predicted FEV_1/FVC <0.7
Gold 2	Moderate	50% ≤ FEV_1 < 80% predicted FEV_1/FVC <0.7
Gold 3	Severe	30% ≤ FEV_1 <50% predicted FEV_1/FVC <0.7
Gold 4	Very Severe	FEV_1 <30% predicted FEV_1/FVC <0.7

As per case WHO estimate nearly 65 million of people are suffering from COPD, this contributes to 5% of all death globally.[2]

Chronic obstructive pulmonary disease is the third leading cause of death worldwide; COPD led to 3.84 million deaths in 2019, a toll expected to reach 4.4 million yearly by 2040. With a worldwide prevalence of 10.1%, COPD afflicts many people in low-income, middle-income and wealthy countries and years of life lost prematurely increased 14.00% between 2007 and 2019. Although COPD is a substantial problem everywhere, China and India accounts for more than 50% of all cases of COPD in the world. COPD is currently the third leading cause of death in the world.[3]

One of the characteristic features of COPD is acute exacerbation, which usually are associated with increased inflammation due to infections (bacterial, viral and combined viral/bacterial) and/ or environmental factors. There is a positive relationship between exacerbations of COPD and hospitalization, decline in quality of life and mortality rate. Early detection of acute exacerbation of COPD is essential to avoid these major complications.[4]Inflammation in COPD may be contributed to many cell types such as the macrophages, the neutrophils and the lymphocytes.[5,6]

Neutrophils play an important role in inflammatory conditions more than macrophages. Neutrophils are important source of proteases, especially reactive oxygen species and neutrophil elastase. They are the hallmark of acute inflammation.[7]

Unlike other inflammatory biomarkers eg. 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 also a rapid, easy method and cost-effective. The neutrophil to lymphocyte ratio (NLR), is a simple ratio that is obtained from the complete blood count of patient, which is found out by dividing absolute neutrophil count as numerator and absolute lymphocyte count as the denominator. So any conditions which alter the counts will change the ratio, which can increase or decrease. The ratio indicates the inflammatory status of the individual that is the cellular mediated inflammatory response. High value of the ratio indicates there is some response to inflammation happening in the body. So many of the conditions NLR can vary and its value can be used in monitoring as a biomarker in those conditions, some are hypertension, diabetes, obesity, metabolic syndromes, cardiovascular disease, renal failure, any chronic malnutrition states, cerebrovascular disease, Alzheimer's, COPD and even in psychiatric conditions- like delirium etc. This parameter can also use in various cancers for monitoring of therapy of drugs, prognosis of treatment with various therapies. The usefulness of NLR as an inflammatory marker can compared to other routinely used inflammatory markers like C-reactive protein, interleukin-1, tumor necrosis factor-α, ESR etc.

Recently, it has been found that the use of NLR in various cancer prognostication including breast cancer, esophageal cancer, pancreatic cancer, colorectal cancers. An elevated preoperative or pretreatment NLR, calculated from peripheral blood tests, was identified as an independent and readily available prognostic biomarker related to poor survival in numerous cancers, including colorectal cancer, breast cancer, gastric cancer and esophageal cancer, renal cell carcinomas and various studies are undergoing in evaluating the same as inflammation is a basic pathogenesis happening in all cancers and in those states the NLR values are altered.

Many studies have reported an increase of NLR during the inflammatory conditions in different diseases such as pancreatitis, inflammatory bowel diseases and acute coronary syndrome.[8–12]

To our knowledge few numbers of studies have been published about the relationship between neutrophil to lymphocyte ratio (NLR) and respiratory diseases.

Our hypothesis is that NLR could be a useful important inflammatory marker that detects the inflammatory status during acute exacerbations of COPD (AECOPD) and could identify early acute exacerbations for early management.

The aim of this study is to evaluate the potential for NLR to be used as a biomarker of COPD exacerbation and to assess the prognostic role of neutrophil counts and NLR in AECOPD.

2. Materials and Methods

The study was conducted on patients attending department of pulmonary medicine in Sardar Patel Medical College Hospital, Bikaner. This was hospital based case control study. We have included hospitalized 100 patient with primary and final diagnosis of AECOPD and 100 patient of stable period of COPD (on OPD basis).This was consecutive sampling. Sample collection started from approval of thesis till December 2020 or till the sample size is achieved (whichever is earlier).

The study has included diagnosed patients of Chronic Obstructive Pulmonary Disease, irrespective of the severity

and duration of disease. Study cases were personally interviewed to get relevant details after getting informed signed consent. Based upon inclusion and exclusion criteria a minimum of 100 cases of each group were selected. An ethical committee approval was taken and consent of study subjects also taken.

2.1. *Inclusion criteria*

1. Those who will give informed consent.
2. Patients of age 40 years or older.
3. Diagnosed cases of COPD with clinical criteria of exacerbation including increased dyspnea, increased sputum volume or sputum purulence, cough.
4. Diagnosed cases of COPD in stable period who had not any significant changes in their symptoms and who did not need any additional treatment.

2.2. *Exclusion criteria*

1. A primary reason for admission other than AECOPD.
2. Patients with history of respiratory disorder other than AECOPD.
3. Patients with any Hematological disease, oncological disease.
4. Patients with Auto-immune disease.
5. Patients with hepatic disease, renal disease, cardiac illness.
6. Patients with any other acute or chronic infections.
7. Patients with dementia.
8. Patients with Diabetes Mellitus, Hypertension on medication.
9. Patients not giving informed consent.

2.3. *Methods of study*

Data was collected using pretest proformas according to the objectives of the study. After getting informed signed consent, detailed history and examination was done in 100 patients of each group included in the study.

Those patients who satisfied all the inclusion and exclusion criteria were selected for the study. The patients were analyzed in two groups of “acute exacerbation” and “stable” as regards their clinical picture. Data were collected from these group and were analyzed by required (chisqure test) statistical test.

3. Observations and Results

Table 2 shows that maximum patients in both groups were found in 45-60 years age group. The mean age in AECOPD group was 63.21±10.12 years and in stable COPD was 62.38±9.65. Both group were comparable.

Table 3 shows that maximum patients in both groups were male. Both group were comparable.

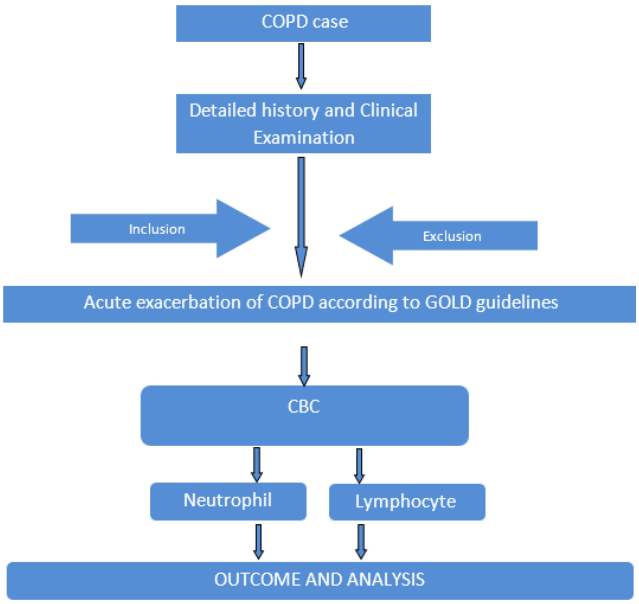

Chart 1: Low chart

Table 2: Age wise distribution of study subject.

Age in years	AECOPD (n=100)	Stable COPD (n=100)	P-value
<45 years	26	27	
45-60 years	60	63	0.515
>60 years	14	10	
Total	100	100	
Mean age in years	63.21±10.12	62.38±9.65	0.412

Table 3: Sex wise distribution of study subject.

Sex	AECOPD (n=100)	Stable COPD (n=100)	P-value
Male	92	85	0.182
Female	8	15	

Table 4: Socio-economic status wise distribution of study subject.

SES	AECOPD	Stable COPD	p -value
Upper	0	0	
Middle	69	70	0.512
Lower	31	30	

Table 4 shows that maximum patients in both groups were from middle class followed by lower socio-economic class. Both group were comparable.

Table 5: BMI wise distribution of study subject.

BMI in kg/mt^2	AECOPD	Stable COPD	P -value
Mean	20.91	21.36	0.01
SD	2.14	3.09	

Table 5 shows that mean BMI significantly lower in AECOPD patients (20.91±2.14 kg/mt^2) as compare to stable COPD patients (21.36±3.09 kg/mt^2).

Table 6: Smoking status wise distribution of study subject.

Smoking	AECOPD	Stable COPD	P-value
Smoker	58	30	
Ex-smoker	32	60	0.025
No smoker	10	10	

Table 6 shows that maximum patients in both groups were smoker. 58.00% patients in AECOPD and in 30.00% patients in stable COPD group were present smoker. The difference in both group was found statistically significant.

Table 7: Pack year wise distribution of study subject.

PACK years	AECOPD	Stable COPD	P-value
0-10 PACK years	3	4	
11-20 PACK years	25	26	
21-30 PACK years	34	38	0.01
>30 PACK years	28	22	
Total	68	40	
Mean pack years	29.52±3.70	23.50±2.05	0.02

Table 7 shows that maximum patients in both groups have used 21-30 pack years. The mean pack years in AECOPD group was 29.52±3.70 and in Stable COPD was 23.50±2.05.

Table 8: Symptoms wise distribution of study subject.

Symptoms	AECOPD	Stable COPD
Breathlessness	100	45
Expectoration	61	41
Cough	72	65
Wheezing	18	15
Chest pain	29	18

Table 8 shows that maximum patients in both groups were presented with cough and breathlessness.

Table 9: mMRC wise distribution of study subject

mMRC grade	AECOPD	Stable COPD	P-value
0	0	0	
1	0	0	
2	0	21	0.001
3	33	59	
4	67	20	

Table 9 shows that maximum patients in AECOPD group was from grade 4 and in stable COPD was from grade 3. The difference in both group was found statistically significant.

Table 10 shows that mean FEV1 was significantly lower in AECOPD patients (42.80±22.15) as compare to stable COPD patients (48.60±20.11). The difference in both groups was found statistically significant.

Table 10: FEV1 wise distribution of study subject

FEV1%	AECOPD	Stable COPD	P-value
Mean	42.80	48.60	0.001
SD	22.15	20.11	

Table 11: Admission per year wise distribution of study subject

Admission per year	AECOPD	Stable COPD	P-value
Mean	1.86	0.86	0.001
SD	0.63	0.63	

Table 11 shows that mean admission per year were significantly higher in AECOPD patients (1.86±0.63 per year) as compare to stable COPD patients (0.86±0.63 per year).

Table 12: GOLD criteria wise distribution of study subject

GOLD stage	AECOPD	Stable COPD	P-value
A	13	25	
B	7	17	0.008
C	26	17	
D	54	41	

Table 12 shows that maximum patients in AECOPD group were from GOLD stage 4 and in stable COPD were also from GOLD stage 4. The difference in both group was found statistically significant.

Table 13: 1Neutrophil count wise distribution of study subject

Neutrophil	AECOPD	Stable COPD	P -value
Mean	11.49	6.47	0.001
SD	2.32	2.01	

Table 13 shows that mean neutrophil count was significantly higher in AECOPD patients (11.49±2.32) as compare to stable COPD patients (6.47±2.01). The difference in both groups was found statistically significant.

Table 14: Lymphocyte count wise distribution of study subject

Lymphocyte	AECOPD	Stable COPD	P-value
Mean	2.07	1.71	0.001
SD	0.05	0.07	

Table 14 shows that mean lymphocyte count was significantly higher in AECOPD patients (2.07±0.05) as compare to stable COPD patients (1.71±0.07). The difference in both groups was found statistically significant.

Table 15 shows that in 67.00% patients of AECOPD group NLR ratio was >5 and in 33.00% patients NLR ratio between 3-5. The difference in both groups was found statistically significant.

Table 15: NLR wise distribution of study subject.

NLR	AECOPD	Stable COPD	P-value
1-3	0	1	
3-5	33	99	0.01
>5	67	0	
Total	100	100	

Table 16: NLR wise distribution of study subject

NLR	AECOPD	Stable COPD	P-value
Mean	5.54	3.77	0.001
SD	2.12	0.22	

Table 16 shows that mean NLR was significantly higher in AECOPD patients (5.54±2.12) as compare to stable COPD patients (3.77±0.22). The difference in both groups was found statistically significant.

Table 17: Outcome wise distribution of study subject

Outcome	AECOPD	Stable COPD	P-value
Death	5	0	0.01
Survived	95	100	

Table 17 shows that 5.00% hospital mortality in AECOPD group.

Table 18: Association between Neutrophil count and outcome in AECOPD patients

Neutrophil	Death	Survived	P-value
Mean	13.21	11.16	0.001
SD	1.24	2.16	

Table 18 shows that mean neutrophil count was significantly higher in death (13.21±1.24) as compare to survived patients (11.16±2.16). The difference in both groups was found statistically significant.

Table 19: Association between NLR and outcome in AECOPD patients

NLR	Death	Survived	P -value
Mean	6.24	5.60	0.001
SD	1.02	1.44	

Table 19 shows that mean NLR was significantly higher in death (6.24±1.02) as compare to survived patients (5.60±1.44). The difference in both groups was found statistically significant.

4. Discussion

The hospital based case control Study was conducted on patients attending department of pulmonary medicine in Sardar Patel Medical College Hospital, Bikaner. We had included hospitalized 100 patients with primary and final diagnosis of AECOPD and 100 patients of stable period of COPD.

AECOPD is associated with increased risk of subsequent exacerbations, worsening of coexisting pathological conditions, poor performance status and physical activity, deterioration of respiratory function and, ultimately, death.[13]

AECOPD is among the most common diseases in clinical practice, especially in patients with infections. Inflammation encompasses a complex network of interactions involving various immune-related cells, including neutrophils and lymphocytes, which can lead to persistent respiratory tissue injury and damage.[14] It has been reported that the absolute counts of key immune-related cell populations in the peripheral blood and their ratios, can adequately reflect chronic inflammatory conditions.[15]

In our study maximum patients in both groups were found in 45-60 years age group. The mean age in AECOPD group was 63.21±10.12 years and in Stable COPD was 62.38±9.65. Maximum patients in both groups were male.

Angus et al.,[16] observed that the incidence of severe sepsis was higher in older population. The mean age of patients with severe sepsis was 63.8 years. In another study conducted by Martin et al.,[17] there was an increased incidence of sepsis by about 20% more in the elderly population compared to younger individuals.[17] The reason for this high incidence among elderly population may be due to the fact that, in recent years life expectancy has increased in general and that with increasing age, individuals develop various co-morbidities like diabetes and malignancy which increase the risk of developing sepsis.

The incidence of sepsis was slightly higher among male patients compared to females. Studies have shown that women appear to be at a lower risk of developing sepsis than men. The reason for this is unclear though in a study Angus et al.,[16] explored and published the possible role of estrogens and androgens that lead to gender differences in the incidence of sepsis.

We could not come to a conclusion based on gender incidence as our study group was small and as there was not much significant difference in male and female incidence.

Our study was compatible with Ercan Kurtipek et al.,[18] who reported that out of the 94 patients, 48COPD with a mean age of 66.65±10.17 years (range: 49-79 years) and 46(49%) patients having acute exacerbation with a mean age of 62.67±9.41 years (range: 48-92 years). Another study by Recai Ergün et al.,[19] reported the mean age of the patients as 69.0±9.2 and 104 (78.2%) of patients weremale.

In our study maximum patients in both groups were from middle class followed by lower socio-economic class. BMI was significantly lower in AECOPD patients (20.91±2.14 kg/mt^2) as compare to stable COPD patients (21.36±3.09 kg/mt^2).

The loss of weight is most likely multifactorial in origin. Established explanations for weight loss in COPD include increased basal metabolic rate due to the increased energy cost of breathing, as well as physical inactivity and malnutrition due to eating difficulties.

Systemic inflammation and hypoxia are particularly prevalent among COPD patients with low body weight.[20] There is increasing evidence that the immune system, in particular inflammatory cytokines, play an important role in the development of weight loss and cachexia. The central cytokine in the loss of muscle mass is TNF-α. TNF-α, which in laboratory animals is associated with accelerated metabolism and protein turnover, was shown to be elevated in the blood of COPD patients suffering from involuntary weight loss.[21,22]

The present study observed that maximum patients in both groups were smoker. 58.00% patients in AECOPD and in 30.00% patients in stable COPD group were present smoker. The difference in both group was found statistically significant. The mean PACK/YR in AECOPD group was 29.52±3.70 and in Stable COPD was 23.50±2.05. The difference in both group was found statistically significant.

Fletcher et al[23] revealed that in susceptible smokers (comparable with the host factors), tobacco smoking is strongly related to chronic bronchitis and airflow obstruction and that these were two different diseases. Cigarette smoking is recognized as the cause of COPD in the vast majority of patients. Although not fully understood, it is widely accepted that an abnormal inflammatory response of the lungs to noxious particles and gases beyond the normal protective inflammatory response is involved in the development of COPD.

In our study maximum patients in AECOPD group were from GOLD stage 4 and in stable COPD were also from GOLD stage 4. The difference in both group was found statistically significant.

Our results supported by a retrospective study done by Taylan et al.[24]

Ercan Kurtipek et al.,[18] who found that among the stable COPD patients, 16(33.3%) were in category B and 18(37.5%) in category D. Among AECOPD patients, 34(73.9%) were in category D, which was conflict of our results.

In present study NLR was significantly higher in AECOPD patients (5.54±2.12) as compare to stable COPD patients (3.77±0.22). The difference in both groups was found statistically significant. Neutrophil count was significantly higher in death (6.24±1.02) as compare to survived patients (5.60±1.44). The difference in both groups was found statistically significant.

Lee et al,[25] found NLR values were significantly higher in patients with COPD exacerbation when compared to those with stable disease and healthy controls (12.4±10.6, 2.4±0.7 and 1.4±0.5, respectively).

Van de Geijn et al,[26] Yao et al,[27] found ROC analysis for using NLR to predict in Xiong et al,[28] observed ROC analysis (AUC 0.91) indicated that a NLR cut-off value of 3.3 predicted mortality with sensitivity of 85.8% and specificity of 89.7%. According to this cut-off point, COPD subjects were divided into a high NLR group and a low NLR group; exacerbations and mortality were significantly lower in the latter group.

5. Summary and Conclusion

The hospital based case control Study was conducted on patients attending department of pulmonary medicine in Sardar Patel Medical College Hospital, Bikaner. We have included hospitalised 100 patients with primary and final diagnosis of AECOPD and 100 patients of stable period of COPD.

Maximum patients in both groups were found in 45-60 yrs age group. The mean age in AECOPD group was 63.21±10.12 years and in Stable COPD was 62.38±9.65yrs. Maximum patients in both groups were male.

Maximum patients in both groups were from middle class followed by lower socio-economic class.

BMI was significantly lower in AECOPD patients (20.91±2.14 kg/mt^2) as compare to stable COPD patients (21.36±3.09 kg/mt^2).

Maximum patients in both groups were smoker. 58.00% patients in AECOPD and in 30.00% patients in stable COPD group were present smoker. The mean PACK/YR in AECOPD group was 29.52±3.70 and in Stable COPD was 23.50±2.05. Maximum patients in AECOPD group were from mMRC grade 4 and in stable COPD were from mMRC grade 3. Maximum patients in both groups were presented with cough and breathlessness.FEV1 was significantly lower in AECOPD patients (42.80±22.15) as compare to stable COPD patients (48.60±20.11). Mean admission per year was significantly higher in AECOPD patients (1.86±0.63 per year) as compare to stable COPD patients (0.86±0.63 per year). Maximum patients in AECOPD group were from GOLD stage 4 and in stable COPD were also from GOLD stage 4. Mean neutrophil count was significantly higher in AECOPD patients (11.49±2.32) as compare to stable COPD patients (6.47±2.01). The difference in both groups was found statically significant. Mean lymphocyte count was significantly higher in AECOPD patients (2.07±0.05) as compare to stable COPD patients (1.71±0.07). The difference in both groups was found statically significant.

Mean NLR was significantly higher in AECOPD patients (5.54±2.12) as compare to stable COPD patients (3.77±0.22). The difference in both groups was found statically significant.5.00% hospital mortality in AECOPD group. Mean neutrophil count was significantly higher in death (13.21±1.24) as compare to survived patients (11.16±2.16). Mean NLR was significantly higher in death

(6.24±1.02) as compare to survived patients (5.60±1.44)

6. Conclusions

Acute exacerbation of COPD (AECOPD), is one of the most common reason of frequent hospitalization in patients with infectious COPD.

NLR is readily available (Available at PHC) and simple parameter, could also be used as a cost-effective marker of inflammation in AECOPD. However, more studies with higher patient series are required in order to highlight the role of NLR in AECOPD patients' response to the treatment and follow-up of exacerbations. But further studies can be conducted to reach better results that can explain the relationship of NLR among patients with COPD and hospitalized in intensive care unit. In our study, we have concluded that the neutrophil lymphocyte ratio on the day of presenting the illness was significantly higher in AECOPD as compare to stable COPD. Those patients who had a high NLR during admission were associated with poor survival.

7. Acknowledgements

None.

8. Conflicts of Interests

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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None.

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