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Neutrophil to Lymphocyte Ratio as A Marker of Acute Exacerbation and Disease Severity in Chronic Obstructive Pulmonary Disease

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) causes obstructed airflow from lungs due to inflammation in the lungs. Due to obstruction in airflow, the patients have difficulty in breathing, Cough, Sputum production and Wheezing. It is caused mainly due to environmental exposure to air particles or due to smoking. There is a high risk for heart disease, lung cancer and other conditions in Patients with COPD. Neutrophil to lymphocyte ratio (NLR) in peripheral blood is a well-known biomarker for inflammatory response. But, the role of NLR in COPD patients is not coherent till now and the present study was aimed to evaluate the usefulness of NLR in patients with COPD. For this purpose, data was collected from 100 patients with COPD and visited Sri Ramakrishna Hospital, Coimbatore for treatment. It was identified from the study that GOLD grading system was highly influenced by Neutrophil Lymphocyte Ratio and mean Neutrophil Lymphocyte Ratio was high in patients with more severe COPD grades of GOLD.NLR increases with increase in severity of COPD in the present study. Survival rate was highly correlated with Neutrophil Lymphocyte Ratio and Neutrophil Lymphocyte Ratio was high for patients who

have less survival rate. NLR increases with decrease in survival rate. Thus, it is concluded that NLR is an effective marker to know its influence on COPD severity but also to know the mortality rate of the Patients.

Keywords: Pulmonary Disease, Neutrophil Lymphocyte Ratio, Inflammation, Survival rate.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the chronic inflammation in the lungs that leads to obstructed airflow from the lungs. There are two common conditions namely Emphysema and Chronic Bronchitis that contribute to COPD. During exacerbations the macrophages and cells lining the mucous membrane produce the inflammatory cytokines which in turn attracts the neutrophils leading to inflammation. Neutrophil to lymphocyte ratio (NLR) is a effortless and basic parameter that is readily obtained from the simplest and easily obtainable complete blood count, even in peripheral hospital. In this study the relationship between NLR and acute exacerbation of COPD which help to assess the severity of the disease, mortality and morbidity of the patients is studied.

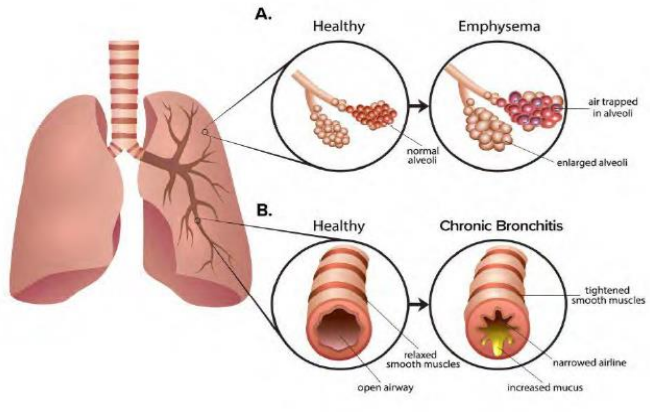


Figure 1: Chronic Bronchitis and Emphysema

Risk Factors

Risk factors for COPD include: Exposure to tobacco smoke, People with asthma, Occupational exposure to dusts and chemicals, Exposure to fumes from burning fuel, Genetics.

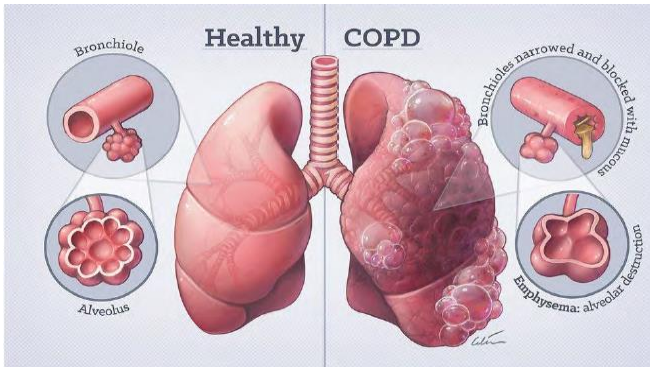


Figure 2: Healthy and COPD lung

Subtypes of COPD

The subtypes of COPD are chronic Bronchitis, Emphysema and Small-Airway Disease.

Chronic Bronchitis

Chronic bronchitis is defined clinically as cough with sputum expectoration for at least 3 months a year for 2 consecutive years. Inflammation in the epithelium of central airways and in mucus producing glands is seen in Chronic Bronchitis.

Emphysema

The enlargement of distal airspaces that are beyond the terminal bronchioles due to destruction of airway walls is called Emphysema. There is a correlation between the degree of Emphysema and smoking, but only 40% of heavy smokers have damaged lungs due to Emphysema. Emphysema is also seen in individuals who have normal lung function. Chronic bronchitis and emphysema can occur simultaneously.

Small-Airway Disease

Airway obstruction in COPD happens in smaller conducting airways and there are structural abnormalities in small airways in smokers with and without COPD. The severity of COPD and the extent of Obstructed are highly correlated.

Pathogenesis of COPD

Initiation

Tobacco smoke causes airway inflammatory reactions inside after minutes or long periods of inhalation. Perhaps the soonest appearance is a break in the vascular and airway barrier function, with lively enrollment of circulating inflammatory cells to the lung. To be sure, oxidants present in the tobacco smoke trigger NF-κ B–dependent inflammatory reactions. The inflammatory responses, by all accounts, to be transient in nature and interceded by NF-κB, possible balanced by administrative organizations that hose NF-κ B–independent reactions.

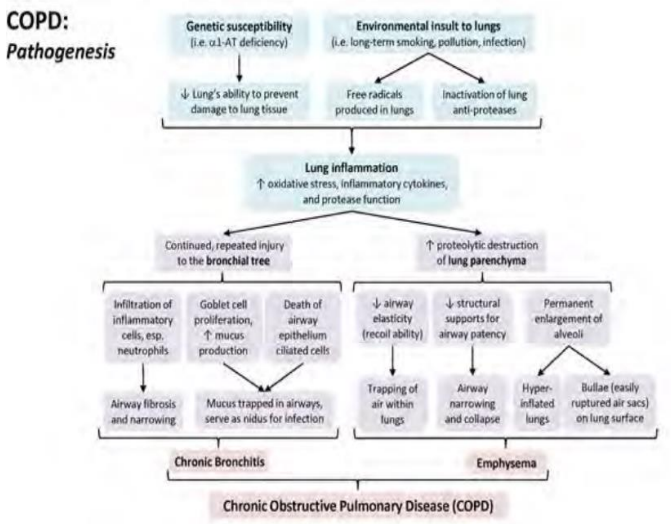


Figure 3: Pathogenesis of COPD

Objectives

- To identify the possible correlation between neutrophil to lymphocyte ratio and severity of COPD.
- To identify correlation between NLR with pulmonary function test (FEV1) in COPD patients.
- To study the prospects of NLR considered to be a cheaper indicator in acute episodes of COPD.

Neutrophil-Lymphocyte Ratio

It has been accounted for that the count of immune related cells in the peripheral blood, and their ratios, can enough reflect chronic inflammatory conditions. Specifically, the neutrophil to lymphocyte proportion (NLR) in peripheral blood is by and large progressively examined as a systemic marker, especially thinking about its rapid, broadly accessible, and generally cheap evaluation through routine blood count investigation. NLR has been demonstrated to be an autonomous prognostic factor in different strong tumors, including lung, colorectal, pancreatic, bosom, ovarian and gastric malignancy.

Materials and Methods

Source of Study

The study is conducted on patients attending Sri Ramakrishna Hospital, Coimbatore during the study period (August 2019 to August 2020). A sum total of 100 patients with Chronic Obstructive Pulmonary Disease attending Sri Ramakrishna Hospital was included in the study, based on the inclusion and exclusion criteria. The study is done after getting informed signed consent from the patients.

Duration of study: 1 Year (August 2019 to August 2020)

Design of Study

Cross Sectional Study

Sample Size Calculation Formula

$$n = \frac{Z^2 p(1-p)}{d^2}$$

n = required sample size

z = confidence level of 95% (standard value of 1.96)

p = expected frequency of factor under study – 7%

d = margin of error 5% (standard value of 0.05)

$$n = \frac{1.96^2 \times 0.07(1-0.07)}{0.05^2}$$

$$= \frac{3.84 \times 0.0651}{0.0025}$$

= 99.99 ~100samples

Method of Sampling

Random Sampling

The study included patients with Chronic Obstructive Pulmonary Disease irrespective of the severity and duration of disease. Study cases are personally interviewed to get relevant details after getting informed signed consent. Based upon inclusion and exclusion criteria minimum of100 cases are selected. An exacerbation of COPD is defined as an onset or worsening of more than two respiratory symptoms (ie, dyspnea, cough or wheeze, sputum amount or purulence) for two or more consecutive days.

Inclusion criteria

Stable diagnosed COPD patients of age 40 years or older male or female who were current or ex-smokers or non-smoker based on clinical history and examination attending Sri Ramakrishna Hospital.

Exclusion criteria

- age < 40 years
- Patients with and diagnosed as Bronchial Asthma, Bronchiectasis or Bullous lung disorders.
- Patients with active pulmonary tuberculosis.
- Patients with malignancy.
- Patients with hepatic disease, renal disease, myocardial infarction.
- Patients with any other acute or chronic infections.
- Patients with pneumonia.
- Patients with dementia.
- Patients with Diabetes Mellitus.
- Patients receiving systemic corticosteroids, antibiotics.
- Patients receiving immune-suppressive treatment.

Methodology

Qualifying patients underwent detail history and clinical examination. Patients' blood counts were estimated at admission.

Statistical Method

The collected Data was analyzed using following statistical methods,

- Diagrammatic representation and Frequency analysis
- Descriptive Statistics such as Mean ± standard deviation
- Independent sample 't' test

Result

The data collected were subjected to Statistical Analysis using SPSS version 22. Frequency analysis, Independent sample 't' test, One way ANOVA and Chi-Square tests were performed for appropriate variables. The probability value, p below 0.05 was 'Significant' and a p value below 0.01 was considered as 'Highly Significant' for all the significance tests. The results of the Statistical analysis are presented in subsequent tables.

Table 1: Age wise Distribution of the Patients

Age in years	No. of Patients	Percent	Cumulative Percent
<50	16	16.0	16.0
51-60	37	37.0	53.0
61-70	36	36.0	89.0
>70	11	11.0	100.0
Total	100	100.0	

Graph 1: Age wise Distribution of the patients

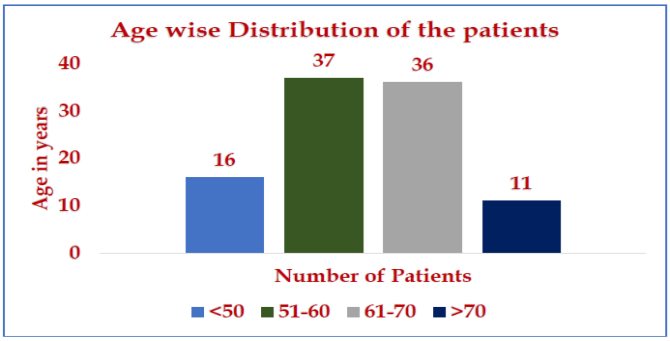


Table 2: Mean Neutrophil Lymphocyte Ratio in different age groups

Age in years	Neutrophil Lymphocyte Ratio		ANOVA 'F' Statistic(p value)
	Mean	Standard Deviation	
<50	2.2563	0.54866	31.777
51-60	3.5827	1.16174	p<0.01
61-70	3.9881	1.22861	Highly Significant
>70	6.3309	0.80163	

Graph 2: Mean Neutrophil Lymphocyte Ratio in different age groups

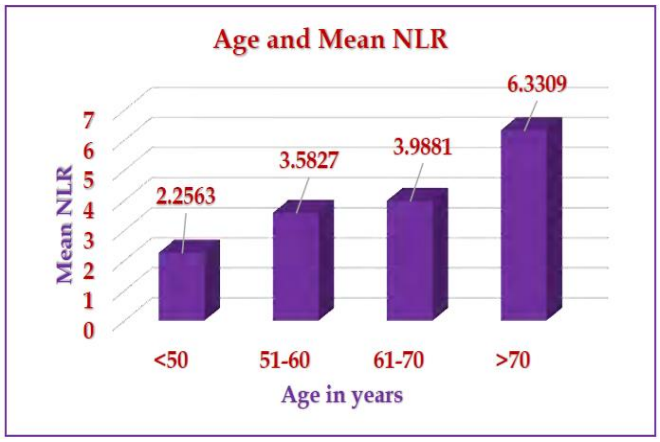


Table 3: Gender wise Distribution of the Patients

Gender	Number of Patients	Percent	Cumulative Percent
Male	95	95.0	95.0
Female	5	5.0	100.0
Total	100	100.0	

Graph 3: Gender wise Distribution of the patients

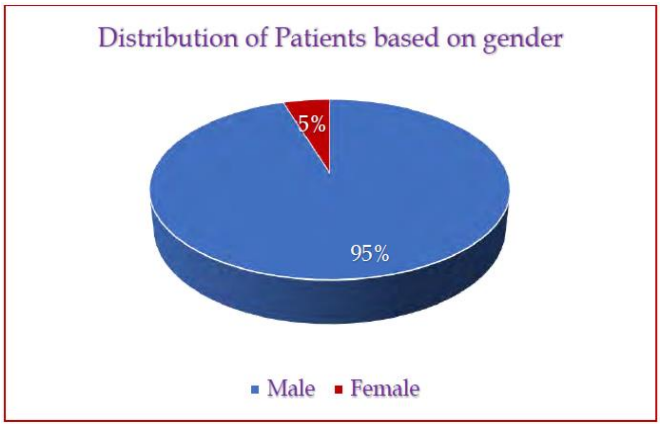


Table 4: Mean Neutrophil Lymphocyte Ratio based on gender

Gender	Neutrophil Lymphocyte Ratio		Independent Sample 't' Statistic (p value)
	Mean	Standard Deviation	
Male	3.7984	1.50508	-0.586
Female	4.2040	1.59857	p>0.05
			Not Significant

Graph 4: Mean Neutrophil Lymphocyte Ratio based on gender

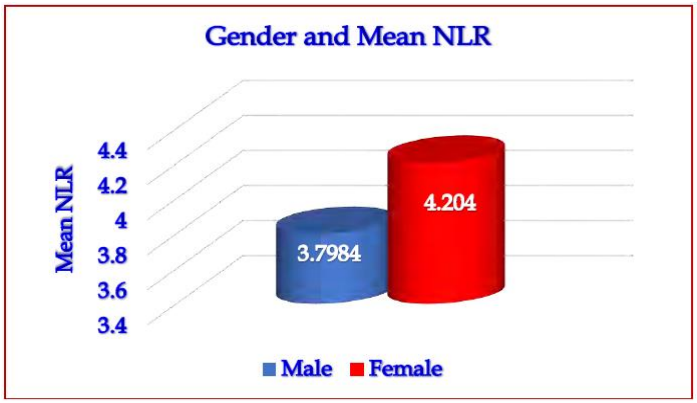


Table 5: Distribution of the Patients based on duration of COPD

Duration in years	No. of Patients	Percent	Cumulative Percent
<5 years	20	20.0	20.0
5-10 years	63	63.0	83.0

>10 years	17	17.0	100.0
Total	100	100.0	

Graph 5: Distribution of the patients based on Duration of COPD

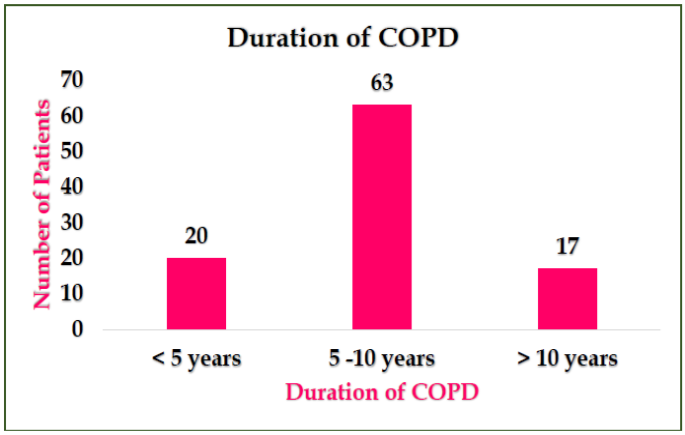


Table 6: Mean Neutrophil Lymphocyte Ratio based on Duration of COPD

Duration in years	Neutrophil Lymphocyte Ratio		ANOVA 'F' Statistic(p value)
	Mean	Standard Deviation	
<5 years	2.1800	0.55521	105.408
5-10 years	3.6890	0.94052	p<0.01
>10years	6.2271	0.78528	Highly Significant

Graph 6: Mean Neutrophil Lymphocyte Ratio based on duration of COPD

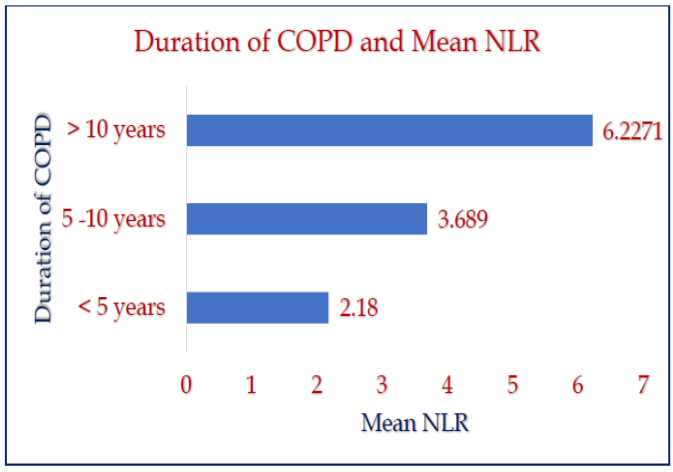


Table 7: Distribution of the Patients based on Smoking Habit

Smoking Habit	No. of Patients	Percent	Cumulative Percent
Yes	66	66.0	66.0
No	34	34.0	100.0
Total	100	100.0	

Graph.7: Distribution of the patients based on Smoking Habit

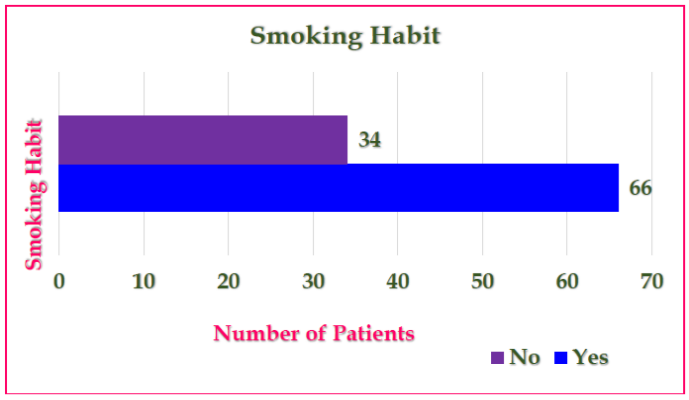


Table 8: Mean Neutrophil Lymphocyte Ratio based on Smoking Habit

Smoking Habit	Neutrophil Lymphocyte Ratio		Independent Sample 't' Statistic (p value)
	Mean	Standard Deviation	
Yes	4.5192	1.19644	8.518 p<0.01
No	2.4588	1.03902	Highly Significant

Graph 8: Mean Neutrophil Lymphocyte Ratio based on Smoking habit

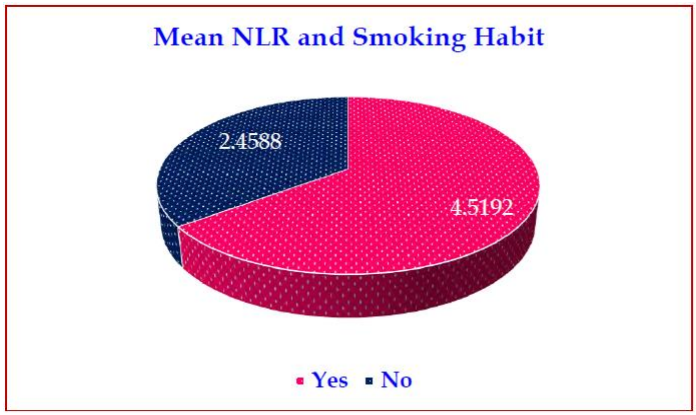


Table 9: Distribution of the Patients based on CT Chest findings

CT Chest findings	Number of Patients	Percent	Cumulative Percent
Emphysema & Cb	62	62.0	62.0
Emphysema	9	9.0	71.0
Chronic Bronchitis	26	26.0	97.0
Normal	3	3.0	100.0
Total	100	100.0	

Graph 9: Distribution of the patients based on CT Chest findings

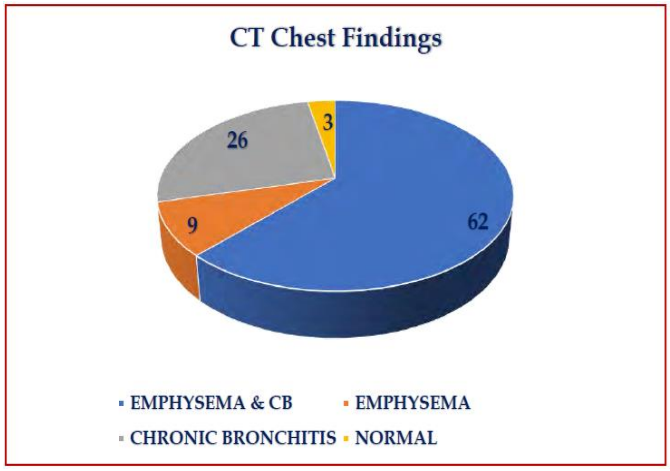
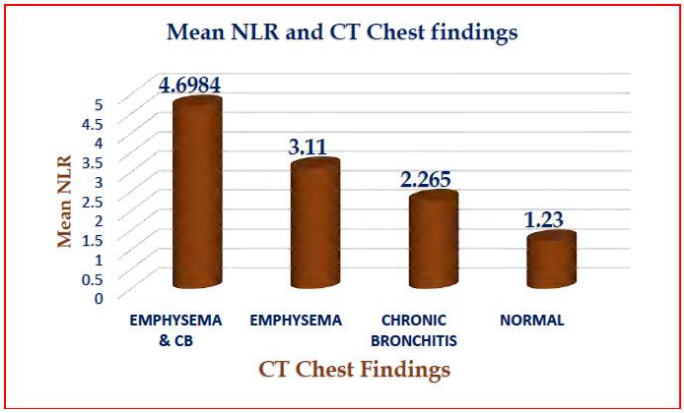


Table 10: Mean Neutrophil Lymphocyte Ratio based on CT Chest findings

CT Chest findings	Neutrophil Lymphocyte Ratio		ANOVA 'F' Statistic(p value)
	Mean	Standard Deviation	
Emphysema & Cb	4.6984	1.17222	48.907
Emphysema	3.1100	0.10112	p<0.01
Chronic Bronchitis	2.2650	0.43146	Highly Significant
Normal	1.2300	0.08660	

Graph 10: Mean Neutrophil Lymphocyte Ratio based on CT Chest findings



Discussion

Age

Majority of the patients (37%) in the study group fall under the age group of 51 to 60 years followed by 36% of them belonging to 61 to 70 years, 16% of the patients below 50 years of age and 11% above 70 years of age. But, in a study by Sakurai et al 1, the mean age of the patients was 72.2 ± 7.9 years and in the study by Arya et al 5 the mean age of the patients was 59.54 ± 11.23 years**.**

Gender

Majority of the patients (95%) in the present study are male and only 5% are female, which is in line with the study by Sakurai et al 1 where 6.2% were female.

Duration of COPD

In the present study, majority of the patients (63%) have COPD for 5 to 10 years, followed by 20% of them for less than 5 years and 17% above 10 years. Similarly, the mean duration of disease in the patients in the study by Arya et al 5was 11.14 ± 5.58 years.

Smoking

Majority of the patients (66%) are Smokers and only 34% are non-smokers. But, in a study by Sakurai et al 1 only 9.6% of the patients were current smokers.

Environmental Exposure

Majority of the patients (56%) in the present study have environmental exposure and only44% do not have hazardous environmental exposure. The mean Neutrophil Lymphocyte ratio for patients who had environmental exposure is 4.8211 ± 1.17162, for patients who did not have environmental exposure is 2.5430 ± 0.69150. It is clear that Neutrophil Lymphocyte Ratio is high in patients who have exposure to hazardous environment.

Biomass fuel Exposure

It is apparent that majority of the patients (58%) have Biomass fuel exposure and only42% do not have Biomass fuel exposure. The mean Neutrophil Lymphocyte ratio for patients who had Biomass fuel exposure is 5.1421 ± 1.07228, for patients who did not have Biomass fuel exposure is 2.8603 ± 0.93623. Thus, Neutrophil Lymphocyte Ratio is high in patients who have exposure to Biomass fuel exposure.

Hypertension

Majority of the patients (65%) in the study group do not have Hypertension and only35% have Hypertension. The mean Neutrophil Lymphocyte ratio for patients who had Hypertension is 4.3869 ± 1.57597, for patients who did not have Hypertension is 3.5128 ±1.38129. It is obvious that Neutrophil Lymphocyte Ratio is high in patients who have Hypertension.

Place of Residence

Majority of the patients (58%) in the present study are from rural area and only 42% are from Urban area. There is no significant association between Neutrophil Lymphocyte Ratio and place of residence in the present study.

Conclusion

The present study has established a relationship between NLR and severity of COPD. The risk factors such as smoking and environmental exposure were correlated with high levels of NLR. The study parameters such as BMI, 6-minute Walking Distance, BODE index, GOLD grades, mMRC grading and FEV1 grades were also highly correlated with NLR. There was highly significant association between severity of disease and NLR levels in the present study. The Consequences of COPD such as Wheezing, Coughing, Clubbing, PAH, fever and Crepitations are also highly associated with NLR levels. NLR is easy to compute that can be obtained from the Complete blood count test. Hence, the present study recommends the use of NLR as a biomarker for stratifications of COPD.

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