Original Research Article

Correlation of Neutrophil lymphocyte ratio with the severity of Chronic obstructive pulmonary disease: A cross-sectional study

Veerendra Arya[1], Akriti Gupta[2*], A.K. Malhotra[3]

[1]Assistant Professor, Department of Medicine, L.N. Medical College and JK Hospital, India
[2]Senior Resident, Department of Physiology, AIIMS Bhopal, India
[3]Professor, Department of Medicine, Dr.RML Hospital, New Delhi, India

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Abstract

Introduction: COPD is the major explanation for mortality and morbidity worldwide.COPD not only affect the lungs and airways but also affect the other part of the body [1].Pulmonary function test (PFT) has been used traditionally for diagnosis and prognosisof Chronic obstructive pulmonary disease, but there are some limitations of PFT. Therefore, it requires to aid some biomarkers for diagnosis and prognosis of COPD. NLR (Neutrophil lymphocyte ratio) can play a potential role in the assessment and prognosis of COPD because it is easily available, low cost, and not difficult to calculate. Enough evidence is available related to systemic inflammation and rise in NLR, like in various diseases such as acute coronary syndrome, inflammatory bowel disease, pancreatitis, and critically ill patients. **Objective:**We are investigating the effectiveness of NLR in assessing the severity of COPD.
Materials and methods: This study was a cross-sectional observational study. It included 57 COPD patients based on inclusion and exclusion criteria. All patients were subjected to routine investigations i.e.- Complete Hemogram, Kidney Function Test, Liver Function Test, Blood Sugar Level, Serum Electrolyte, ECG, X-Ray Chest, 2d echo, ABG, PFT, and TFT.**Result :** Nineteen patients were found to have grade 1COPD; 20 patients grade 2 and 18 patients were of grade 3 of gold stage criteria of COPD. The mean NLR value are 2.79 ± 0.8, 3.11 ± 0.76, 2.9 ±0.77 respectively, ($p > 0.05$). Spearman rank correlation coefficient indicated non-significant correlation of NLR with grade of severity of COPD patients ($p>0.05$).**Conclusion :** The study has revealed there is no correlation between rise in NLR and severity of COPD. SoNLR ratio cannot serve as a marker to detect the severity of COPD. However, NLR can predict the infection and exacerbation of COPD which is an established fact.

Keywords: Chronic obstructive pulmonary disease, C-reactive protein (CRP), Lymphocyte, Neutrophil, Pulmonary function test.

Introduction

COPD is the major explanation for mortality and morbidity worldwide.COPD not only affects the lungs and airways but also affects the other parts of the body[1].COPD is a preventable disease which is characterized by persistent airflow limitation that is progressive, associated with chronic inflammatory response in the airways to noxious particles and gases.(GOLD) "Chronic obstructive pulmonary disease is defined as a disease state characterized by airflow limitation that is not fully reversible" (http://www. gold copd.com/) [2]. This is not truly a disease but a gaggle of diseases. It consists ofchronic bronchitis, emphysema, and small airway disease.In the adult aged ≥ 40years,the global prevalence of COPD (gold stage ≥ 2) is around 9-10% [3].It has been noted that there is a complex persistent inflammatory response within the airways that plays a key role in the pathogenesis of COPD. This inflammation occurs in response to inhaled noxious gases or particles[4,5].A large number of inflammatory markers are involved in the chronic inflammatory phase of COPD which has certain

**Correspondence*
Dr. Akriti Gupta
Senior Resident, Department of Physiology, AIIMS, Bhopal, M.P., India.
E-mail: akriti.srphysiology@aiimsbhopal.edu.in

extrapulmonary effects and may be involved in the severity of COPD along with other different complications [6]. There is the involvement of various inflammatory markers such as C-reactive protein (CRP), fibrinogen and leukocyte counts have been noted with COPD[7,8]. It is advocated that the adverse outcome of COPD can be predicted by the elevated level of CRP, it also predicts the development of cardiovascular complication such as atherosclerosis [9]. Pulmonary function test has traditionally been used to determine the severity of the COPD and progression as well. The limitation with the Pulmonary function test is that it cannot correlate reliably with the state of inflammation and it cannot be performed in the state of acute exacerbation [10,11].Therefore, some extra measures such as biomarkers are required to aid with the diagnosis and prognosis [8,12]NLR (Neutrophil lymphocyte ratio) can play a potential role in the assessment and prognosis of COPD because it is easily available, low cost, and not difficult to calculate. Enough evidence is available related to systemic inflammation and NLR, like in various diseases such as acute coronary syndrome, inflammatory bowel disease, pancreatitis, and critically ill patients [13-16]. We are investigating the effectiveness of NLR in assessing the severity and early exacerbation of COPD.

Materials and methods

This study was a cross-sectional observational study. It is conducted between the period of November 2014 to March 2016. This study protocol was approved by the Institutional review board and ethical committee. It included 57 COPD patients based on inclusion and exclusion criteria. The study cases were recruited from OPD and those admitted in the department of medicine at PGIMER & Dr. Ram Manohar Lohia Hospital, New Delhi. Patients who consented to join the study were informed about the purpose and method of the study. And informed consent was taken.

Inclusion criteria • All COPD patients>18 years of age coming to Dr. Ram Manohar Lohia hospital New Delhi.

Exclusion criteria • All patients with past history of heart disease (like valvular heart disease, coronary artery disease, hypertensive heart disease) • Patients with other respiratory disorders (Restrictive lung disease, lung carcinoma, bronchial asthma) • Electrolyte imbalance. • Thyroid dysfunction. • Feature suggestive of obstructive sleep apnoea. • Patients with hepatic and renal dysfunction.

Patients with symptoms of COPD were subjected to a spirometry tests to confirm the diagnosis All subjects who qualified the criteria for the diagnosis of COPD were included after informed consent. A detailed history including age, sex, smoking history, presenting complaints, and history of presenting complaints were taken. History of the presence of comorbidities was taken including diabetes mellitus, hypertension, coronary artery disease, thyroid disorder, obstructive sleep apnoea, hepatic disease, renal disease. Detailed general physical examination and systemic examination was done in all the patients. Patients with comorbidity as mentioned above were not included in the study.

Pulmonary function test by jaegers spiro pro spirometer; - Pulmonary function test was performed with standard protocol at respiratory laboratory Dr. RML hospital New Delhi by Jaegers Spiropro compact spirometer

Instruction - Patients were instructed to avoid alcohol for a minimum of 4 hours,Smoking for at least 1-hour, Heavy exercise for at least 30 minutes, Heavy meal within 2 hoursbefore the test.

Procedure :Patient were said to sit upright on an armed chair in a sitting position with flat foot on floor with uncrossed leg.

Technique Before performing the forced expiration, tidal (normal) breaths can be taken first, then a deep breath taken in while still using the mouthpiece, followed by a further quick, full inspiration. Alternatively, a deep breath can be taken in then the mouth placed tightly around the mouthpiece before a full expiration is performed.

The patient can be asked to completely empty their lungs then take in a quick full inspiration, followed by a full expiration.

2D echo was done to rule out a cardiac disease like valvular heart disease, hypertensive heart disease, and coronary artery disease.

Laboratory measurements:With informed consent, blood samples were collected from patients with COPD. ABG (Arterial blood gas analysis) was performed on arterial blood samples from the patients with COPD while they were breathing in room air.

All fifty-seven patients were subjected to routine investigations i.e.- 1. Complete Hemogram 2. Kidney Function Test 3. Liver Function Test 4. Blood Sugar Level 5. Serum Electrolyte 6. ECG 7. X-Ray Chest 8. Thyroid Function Test 9. Serum Measurements of T3 T4 TSH were performed by chemiluminescence method.

Statistical analysis:The presentation of the continuous variables was done as mean ± SD and median values. The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not

normal, we used non parametric tests. The following statistical tests were applied for the results:

1. The association of the variables which were quantitative in nature were analyzed using Kruskal Wallis test.
2. Spearman rank correlation coefficient was used to correlate NLR with grade of severity.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software ver 21.0.For statistical significance, p value of less than 0.05 was considered as significant.

Results

The study was carried out on 57 patients of COPD (according to GOLD criteria) in the department of medicine and cardiology PGIMER & Dr. RML Hospital New Delhi. All the patients of COPD were examined, investigated, and then they were selected for the study according to the pre-defined inclusion and exclusion criteria. Demographic and laboratory characteristics of study participants shown in Table 1. Nineteen patients were of grade 1, 20 patients were of grade 2 and 18 patients were of grade 3 of gold stage criteria of COPD.The mean NLR value are2.79 ± 0.8, 3.11 ± 0.76, 2.9 ±0.77 respectively, ($p > 0.05$) Table 2. Spearman rank correlation coefficient indicated non-significant correlation of NLR with grade of severity of COPD patients ($p>0.05$) Table 3.

Table 1:**The demographic and laboratory characteristics of study participants**

	Mean ± SD	Median	Min-Max	Inter quartile Range
AGE(years)	59.54 ± 11.23	60	30-81	51.750 - 68.250
Duration of disease(years)	11.14 ± 5.58	12	2-25	6 – 15
HR(per min)	100.4 ± 11.57	101	79-119	92 - 109.500
SBP(mmHg)	129.75 ± 8.69	130	100-142	125.500 – 136
DBP(mmHg)	74.81 ± 7.38	76	60-90	70 – 80
PH	7.39 ± 0.06	7.39	7.2-7.57	7.360 - 7.410
PCO2(mmHg)	46.6 ± 5.28	46	34-63	43 – 49
PO2(mmHg)	88.54 ± 8.19	89	62-99	83 – 96
SPO2%	91.18 ± 6.63	92	72-99	88.750 – 97
HB (gm %)	13.33 ± 1.28	13.5	10.8-15.6	12.300 - 14.350
TLC	8550.7 ± 2014.13	8700	4900-12000	6925 – 10500
RBS(mg/dl)	122.53 ± 21.9	119	82-172	110.750 - 140.250
U(mg/dl)	35.12 ± 10.51	31	16-61	26 - 43.500
Cr(mg/dl)	0.56 ± 0.3	0.6	0.1-1.2	0.300 - 0.800
Na(mmol/L)	139.6 ± 3.86	140	131-147	136 - 142.250
K(mmol/L)	3.95 ± 0.34	3.9	2.9-4.7	3.800 - 4.200
Total Bilrubin (mg/dl)	0.82 ± 0.24	0.8	0.3-1.6	0.600 - 0.900
D. Bilrubin (mg/dl)	0.24 ± 0.13	0.2	0.1-0.8	0.175 - 0.300
InD. Bilrubin(mg/dl)	0.58 ± 0.18	0.6	0.2-1	0.400 - 0.700
TSH(U/ml)	3.32 ± 1.1	3.8	0.9-4.6	2.575 - 4.225
T4(mcg/dl)	1.9 ± 0.55	1.9	1-2.9	1.475 - 2.325
T3(ng/dl)	77.44 ± 14.57	79	41-112	66.500 – 89
FEV1%	62.28 ± 18.11	61	30-86	49 – 81
FEV1/FVC%	65.14 ± 5.58	67	37-69	63 – 68

Table 2: Association of NLR ratio with grade of severity

NLR ratio	Grade1(n=19)	Grade2(n=20)	Grade 3 (n=18)	Total	P value	Test performed
Mean ± SD	2.79 ± 0.8	3.11 ± 0.76	2.8 ± 0.73	2.9 ±0.77	0.371	Kruskal Wallis test; Chi square=1.983
Median(IQR)	2.57(2.1-3.255)	3.16(2.44-3.85)	2.84(2.055-3.26)	3(2.22-3.54)		
Range	1.87-4.44	1.8-4.15	1.81-3.95	1.8-4.44		

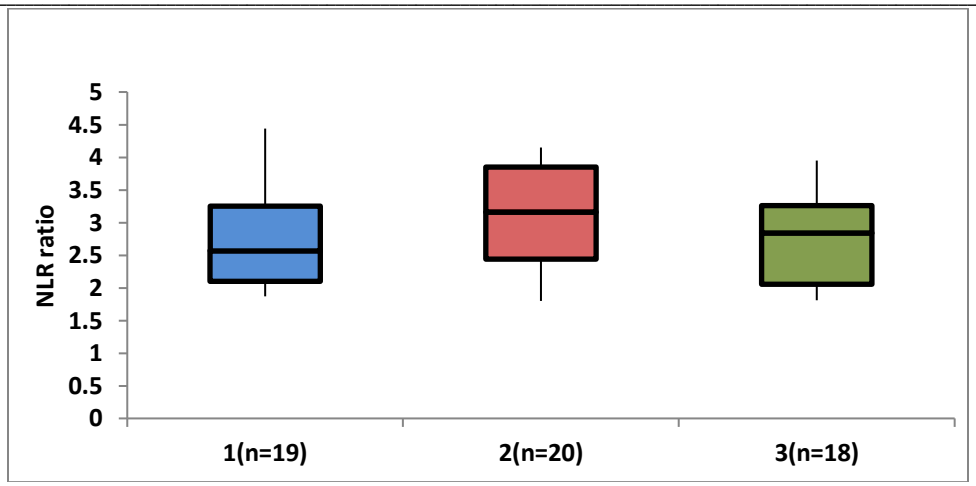

Fig 1:Association of NLR ratio with grade of severity.(non-parametric variable, Box-whisker plot)

Table 3: Correlation of NLR ratio with grade of severity

Variables	Grade of severity
NLR ratio	
Correlation coefficient	0.012
P value	0.929

Spearman rank correlation coefficient

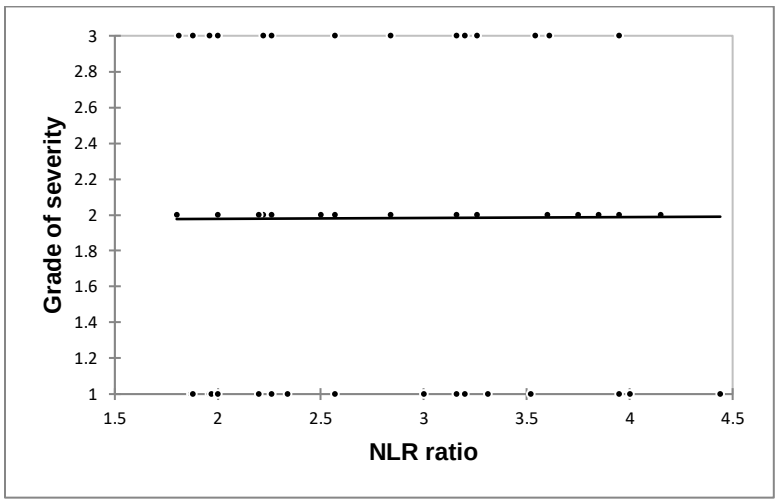

Fig 2:Correlation of NLR ratio with grade of severity

Discussion

Some recent studies have shown the association of decreased pulmonary function with increase in inflammatory markers such as fibrinogen sputum neutrophils myeloperoxidases, fibrinogen, and some acute-phase proteins such as CRP in COPD [17]. Furthermore, a low-grade inflammation that has been demonstrated by an increase in blood leukocyte levels, acute phase proteins, and other inflammatory cytokines is also associated with stable COPD [18].

COPD involves local airway and systemic inflammation. The clinical course of the disease can be classified into the stable phase and acute exacerbation. During the stable phase, this low-grade systemic inflammation induces mild activation of various circulating inflammatory cells and inflammatory proteins while during exacerbation increased level of these inflammatory markers has been reported.It has been reported recently that a decline in pulmonary function causes an elevation in the inflammatory markers including sputum neutrophils,

myeloperoxidases, fibrinogen, and some acute-phase proteins such as CRP in COPD patients [17]. Mild systemic inflammation during stable phase COPD leads to an increase in blood leukocyte counts, acute phase proteins, and other inflammatory cytokines[18].Elevated leukocyte counts and their subtypes have been investigated as markers of inflammation in chronic inflammatory diseases [8,19-20]. NLR is found to be more sensitive than total leukocyte counts in chronic inflammatory diseases like pancreatitis [14].Previous studies have found a positive correlation of rise in NLR with acute exacerbation of COPD. In our study, we have not included patients with exacerbation of COPD, and we did not find the correlation of NLR with the severity of COPD. While Gunay et al. found a significant positive correlation between CRP and NLR levels in COPD patients at stable periods and patients during acute exacerbation [21].In the same study, they also did not find any relation of NLR with the severity of COPD in stable COPD patients.Furutate et al. conducted a study of 141 COPD patients and found a positive association between the NLR and clinical parameters in stable COPD patients [22]. In a prospective study conducted by Lee et al. [23] on 59 patients with COPD exacerbation, 61 patients with stable disease, and 28 healthy controls, they observed NLR values were significantly higher in patients suffering from acute exacerbation of COPD as compared to stable COPD patients and healthy volunteers. NLR can be a predictor of acute exacerbation of COPD but it is not strongly correlated with the severity of COPD among stable COPD patients.NLR is an upcoming parameter that indicates systemic inflammation it is a cost-effective, rapid, and widely available parameter. Further study is required with a large study population in order to find its usefulness in stable COPD patients.

Limitation

One limitation of our study was that study not included the participants with acute exacerbation of COPD and the control group.

Conclusion

The study was conducted on patients with stable COPD in a different stage of severity which has shown that NLR ratio is not associated with the severity of COPD. In comparison to another study which has shown a positive correlation of NLR with acute exacerbation of COPD which might be due to infection which has caused exacerbation, not due to disease itself. Further study required to find out the correlation with a large sample size. NLR ratio cannot be used as a marker to detect the severity of COPD. However, NRL can predict the infection and exacerbation of COPD**.**

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