Journal of Cardiovascular Disease Research
ISSN: 0975-3583,0976-2833 VOL 15, ISSUE 11, 2024

Original Research

Role Of Inflammatory Markers In Acute Exacerbation Of Chronic Obstructive Pulmonary Disease

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Received Date:16 September 2024 Accepted Date: 25 October 2024

Abstract:
Background It is estimated that there are around 3 million deaths annually due to COPD worldwide. According to WHO COPD is 3rd leading causes of death worldwide.

COPD is characterized by progressive destruction of the pulmonary parenchyma frequently. The result of response to external stimuli (i.e long term exposure of cigarette smoking, environmental pollution) which culminates the progressive airway limitation. Inflammation in COPD may play a role via various cell type like neutrophil ,macrophages and lymphocyte. In this regard scientist have devoted their attention to the ratio of some of inflammatory markers as for examples, neutrophil to lymphocyte Ratio and platelet to lymphocyte ratio to know the role in systemic inflammation.

METHOD : This prospective observational study was conducted in 50 individual who were either admitted or visited as an out-patient basis in medical ward of Guru Nanak Dev Hospital, attached with Government Medical College, Amritsar, with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) during the 1 year study period (1ST January 2023 to 31ST December 2023). Patients with acute exacerbation was investigated for levels of inflammatory markers. The study was carried out after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. Written informed consent was obtained from the patients. The nature of study was explained to each patient in their vernacular language, and informed consent was taken from all who fulfilled the inclusion criteria and were willing to participate in the study.

RESULT: In our study 50 cases of COPD were included from OPD and IPD of GNDH Amritsar. These all were having exacerbation symptoms of COPD. We enrolled 31 male patients and 19 female patients. NLR values showed positive correlation with AECOPD having higher mean noted in GOLD category (28.20) which is significant, overall mean was 13.8 with p value(.043) which is significant.

CRP value also showed positive correlation with mean of 41.76 with p value of (0.00) which is significant, PLR highest mean was found in GOLD category 4 of COPD ,overall mean 170.06 having p value (0.00). Procalcitonin level was found highest in GOLD category 3 with mean value of 0.32 which have p value (0.000).

Conclusion:
Hence our study showed that these biomarkers do have a role in predicting the AECOPD which can help in predicting the risk stratification and _proper management plan of treatment n AECOPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive breathing difficulty and airway limitation, is considered one of the main disease in present time1. It's estimated that there are around 3 million deaths annually due to COPD worldwide2. According to World Health Organization (WHO) COPD is the third leading cause of death worldwide. With the increasing frequency of smoking in developing countries and growing populations in high- income countries, the frequency of COPD is anticipated to rise over the coming years up to 40 times, and by year 2060, there may be over 54 lakhs deaths annually because of COPD and other associated conditions.3,4.

In India, the prevalence of COPD is alarmingly high (approximately 7.4
%) with a men to women ratio of 1.56:1 in population of over 35 years of age.5 The GOLD guidelines defines COPD as “a common preventable and treatable condition, which is characterised by continuous airway limitation and also progressive. It is also associated with increased inflammatory response in the airways and the lungs to various particles and gases”.6

COPD is characterised by a progressive destruction of the pulmonary parenchyma, frequently the result of response to external stimulants (i.e. long- term exposure to cigarette smoking, environmental pollution), which culminates in progressive airway limitation. Typical clinical manifestations include chronic bronchitis, which is caused by inflammation of airways and remodelling, and emphysema which is a disease of the lower airways

and the lung tissue. It is characterised by difficulty in breathing and productive cough. It can progress over time to chronic hypoxemic and/ or hypercapnic respiratory failure. COPD is frequently characterised by extra pulmonary manifestations, such as systemic inflammation, cardiovascular comorbidities, cancer, muscle dysfunction, osteoporosis, anaemia, depression and anxiety. These can also contribute to disability and mortality.7

"A sustained worsening of the case's condition, from the stable state and beyond normal day-to-day variations, that's acute in onset and necessitates a change in regular drug regimen," is the definition of an acute exacerbation of COPD (AECOPD).8 It's characterised by increased breathlessness, frequently accompanied by respiratory distress, increased cough and expectoratation, change in colour of expectoratation and fever. Generally, exacerbations are complicated by secondary infection and air pollution. Acute exacerbations are a cause of severe respiratory failure in COPD cases, that warrant hospitalisation and constitute significant socio-profitable burden.6 Acute exacerbation, is generally associated with an increased environmental associated inflammation, isolated viral, bacterial, or mixed infections. Acute exacerbation of chronic obstructive pulmonary complaint (AECOPD) is significantly associated with hospitalization, decreased quality of life, and increased mortality. Thus, a timely anticipation of AECOPD seems necessary to help the prevent above complications.8

There are numerous etiological factors behind the acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and the pathogenesis has been known to be complex in these cases. numerous studies have revealed that 80 percent cases of AECOPD were caused by viral or bacterial infection, of which 50 percent caused by the bacterial infections.9-11 Although the potential role of bacterial infection in acute exacerbation of COPD is still controversial.10 Lower respiratory tract infection with acute exacerbation is the leading cause of death in cases with moderate to severeCOPD.11-14 The pathogenesis of COPD isn't yet completely understood. It has been extensively accepted that COPD is characterized by persistent inflammation of the airways, pulmonary parenchyma pulmonary vessels, along with a variety of media released by inflammatory cells.15

Cases with chronic obstructive pulmonary disease (COPD) have defective functional status of lungs.16-18 There is substantial proof that

increased number of exacerbations is associated with health status impairment.19 The degree of dyspnoea using the Medical Research Council (MRC) dyspnoea scale has been linked as a stronger predictor of 5 year mortality than the forced expiratory volume in one second (FEV1), and measures of health status and inability to exercise are very much associated with mortality. Although severity of COPD is mostly assessed using measures of lung function – generally FEV1 – although functional status in COPD bears little or no relationship with FEV1. In the treatment of COPD, assessment of exercise intolerance and health status may prove unrealistic; hence there is a need for simple biomarkers for assessing the severity.20

Inflammation in COPD may play a role via various cell types like macrophages, neutrophils, and lymphocytes.8 Neutrophils, as compared with macrophages; play an important part in inflammation. In Neutrophils, especially reactive oxygen species and neutrophil elastase, are main sources of proteases which are markers of acute inflammation.21 In this regard, scientists have devoted their attention to the ratio of some of inflammatory markers as for example the neutrophil- to- lymphocyte ratio (NLR) and platelet- to- lymphocyte ratio(PLR) to know their role in systemic inflammation .21- 23

NLR calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, serves as a simple yet effective indicator of systemic inflammation. Elevated NLR levels have been associated with increased disease severity, exacerbation risk, and poorer prognosis in COPD patients. Moreover, NLR correlates with various clinical parameters, such as forced expiratory volume in one second (FEV1) and COPD Assessment Test (CAT) scores, providing valuable insights into disease activity and progression.25

Platelets, primarily known for their role in hemostasis and thrombosis, also exert significant immunomodulatory effects, contributing to inflammation and immune response regulation. PLR, which is calculated by dividing the absolute platelet count by the absolute

lymphocyte count, has gained attention as a potential marker of systemic inflammation. Elevated PLR levels have been linked to increased airway inflammation, exacerbation frequency, and cardiovascular comorbidities in COPD patients.26 Furthermore, PLR has shown associations with disease severity indices, such as the BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity), suggesting its utility as a prognostic tool in COPD management. Since its levels rise sharply in response to inflammation, infection, trauma, necrosis, and autoimmune illnesses, CRP is classified as an acute-phase reactant. An elevated CRP level does not diagnose a specific disease; however, it is a sensitive and accurate reflection of acute phase response. The PCT is a peptide precursor of the hormone calcitonin, which is involved with calcium homeostasis. In severe infection, the blood levels of PCT may rise up to 100 ng/mL. Measurement of PCT can be used as a marker of severe sepsis and generally correlates well with the degree of sepsis.7

Despite individual studies demonstrating the potential utility of these biomarkers in predicting AECOPD, the combined assessment of NLR, PLR, CRP, and procalcitonin as predictors of exacerbation onset and severity

remains relatively unexplored. This study aims to identify the possible correlation between NLR, PLR, CRP, and procalcitonin levels as predictors of AECOPD in patients with COPD.

MATERIALS AND METHODS

This prospective observational study was conducted in 50 individual who were either admitted or visited as an out-patient basis in medical ward of Guru Nanak Dev Hospital, attached with Government Medical College, Amritsar, with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) during the 1 year study period (1ST January 2023 to 31ST December 2023). Patients with acute exacerbation was investigated for levels of inflammatory markers. The study was carried out after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. Written informed consent was obtained from the patients. The nature of study was explained to each patient in their vernacular language, and informed consent was taken from all who fulfilled the inclusion criteria and were willing to participate in the study.

METHOD OF DATA COLLECTION :

Study Design: A Prospective observational study

Sample Size: 50 patients of acute exacerbation chronic obstructive pulmonary disease

The study included patients with 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 50 cases were selected. An exacerbation of COPD was defined as an onset or worsening of more than two respiratory symptoms (i.e., dyspnea, cough or wheeze, sputum amount or purulence) for two or more consecutive days.

INCLUSION CRITERIA :

•Patients of COPD who were diagnosed on the basis of Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and were in acute exacerbation.22

EXCLUSION CRITERIA:

1. Patients with Bronchial Asthma, Bronchiectasis.
2. Patients with active pulmonary tuberculosis.
3. Patients with malignancy.
4. Patient with the history of treatment with steroids in the last three months.
5. Patients with pneumonia.
6. Patients who were unable to perform spirometry.

METHOD OF STUDY:

Data was collected using pre-test proformas according to the objectives of the study. After getting informed signed consent detailed history and examination was done in 50 patients included in the study. The aim and purpose of study was informed to the patients and their informed consent was taken.

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) was determined on the basis of complete blood count (CBC).

Those patients who satisfy all the inclusion and exclusion criteria was selected for the study.

1. Investigations performed were :

- Complete Blood Count.
- Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) was determined on the basis of complete blood count (CBC).

1. Blood Sugar.
2. Blood Urea.
3. Serum Creatinine.
4. Serum Electrolytes (sodium, potassium)
5. C-Reactive Protein.
6. Serum procalcitonin.
7. Electrocardiography (ECG).
8. Pulmonary function test.
9. Sputum AFB, Sputum culture and Sensitivity (if needed).
10. CT Scan of Chest
11. Chest X-ray
12. Renal Function Tests (Blood Urea, Serum Creatinine)

Detailed clinical examination of each and every patient was recorded in proforma.

DATA ANALYSIS:
The data was collected systematically and after entering in Microsoft excel sheet, it was analyzed using appropriate statistical software. Continuous variables was expressed as mean±S.D. and categorized variables as counts and percentage.

RESULTS
In our study 50 cases of COPD were included from OPD and IPD of GNDH Amritsar .these all were having exacerbation symptoms of COPD enrolled 31 male patients and 19 female patients. NLR values showed positive correlation with AECOPD having higher mean noted in GOLD category (28.20) which is significant, overall mean was 13.8 with p value(.043) which is significant. CRP value also showed positive correlation with mean of 41.76 with p value of (0.00) which is significant, PLR highest mean was found in GOLD category 4 of COPD ,overall mean 170.06 having p value (0.00). Procalcitonin level found highest in GOLD category 3 with mean value of 0.32 which have p value (0.000).

TABLE 1: SYMPTOMS

	Frequency	Percent
Breathlessness	46	92.0
Cough	7	14.0
Chest pain	4	8.0
Fever	2	4.0

Table 1: Among the patients, symptoms were reported and it was found that majority of patients had breathlessness (92%) followed by cough (14%), chest pain (8%) and fever (4%).

Graph 1: Symptoms

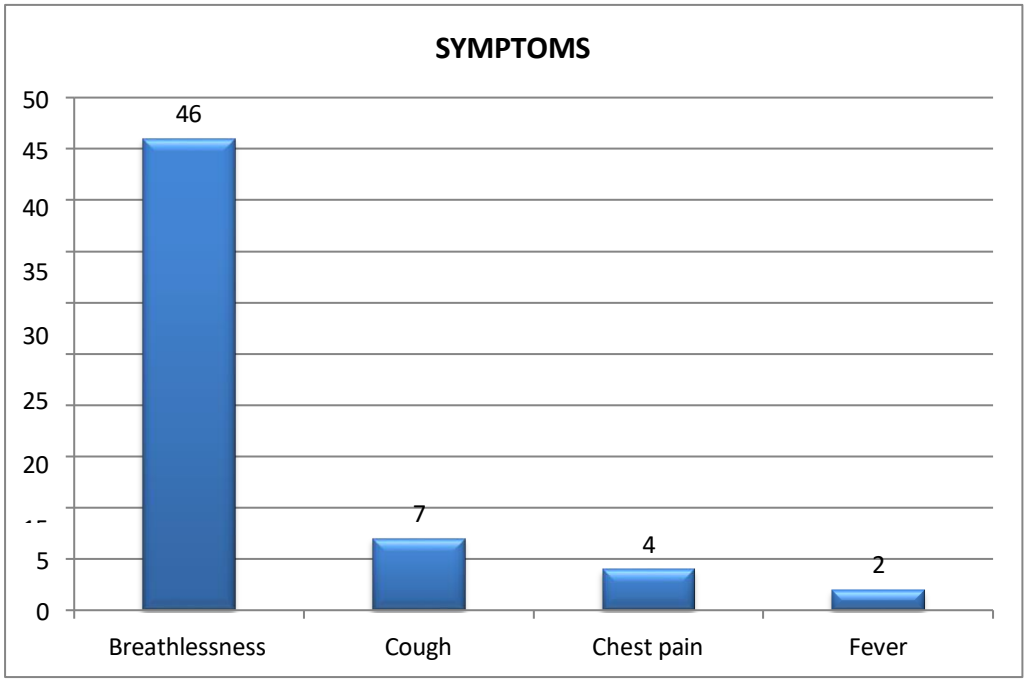
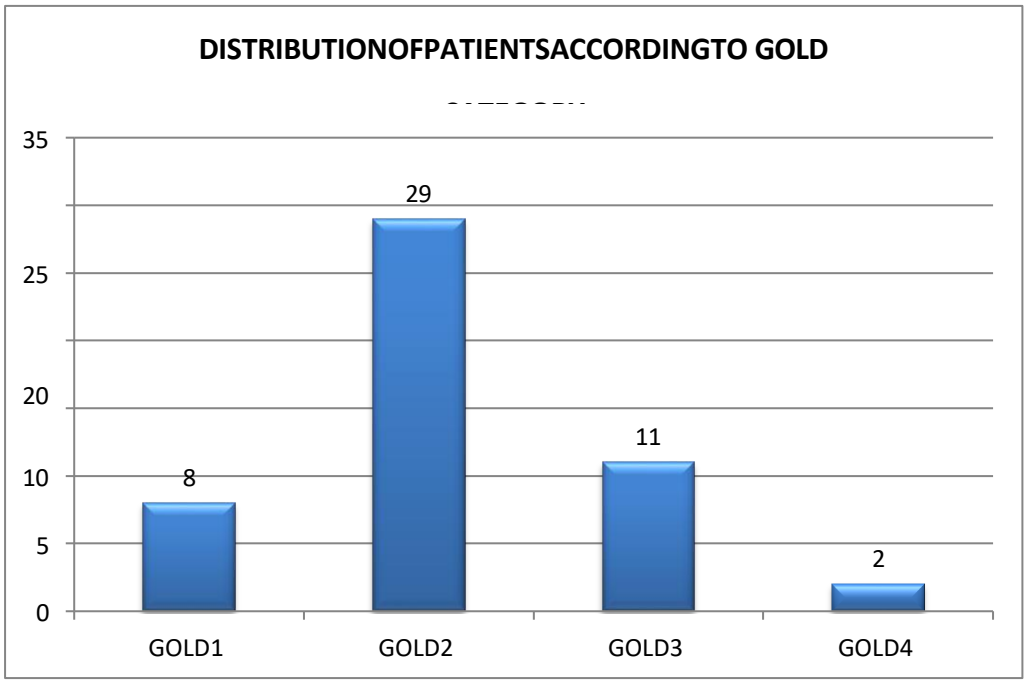


Table 2: Distribution Of Patients According To Gold Category

	Frequency	Percent
GOLD 1	8	16.0
GOLD 2	29	58.0
GOLD 3	11	22.0
GOLD 4	2	4.0
Total	50	100.0

Table 2: When GOLD category was analyzed, it was found that majority of patients (58%) fell under GOLD category 2 followed by GOLD 3 category (22%), GOLD 1 (16%) and 4% in GOLD 4 category.



Graph 2: Distribution Of Patients According To Gold Category

Table 3: Comparison Of Inflammatory Markers Across Gold Categories

	Gold Category	N	Mean	Std. Deviation	Minimum	Maximum	P value
NLR	1	8	4.91	2.11	3.36	9.66	0.043
	2	29	17.44	19.57	2.04	64.66	
	3	11	7.94	3.03	4.11	11.23	
	4	3	28.92	0.00	28.92	28.92	
	Total	50	13.80	16.09	2.04	64.66	
PLR	1	8	87.34	62.06	47.58	214.95	0.000.
	2	29	186.20	121.12	50.84	440.12	
	3	11	123.00	35.89	83.21	177.50	
	4	2	525.86	0.00	525.86	525.86	
	Total	50	170.06	127.01	47.58	525.86	
CRP	1	6	49.75	39.24	4.00	116.00	0.000
	2	31	39.10	30.62	4.00	104.00	
	3	11	48.00	48.98	6.00	126.00	
	4	2	14.00	0.00	14.00	14.00	
	Total	50	41.76	36.06	4.00	126.00	
Procalcitonin (ng/ml)	1	6	0.27	0.157	0.13	0.51	0.000
	2	31	0.30	0.237	0.11	0.90	
	3	11	0.41	0.301	0.12	0.90	
	4	2	0.24	0.049	0.21	0.28	
	Total	50	0.32	0.239	0.11	0.90	

Table 7: When parameters were analyzed against the GOLD category, it was found that highest mean in NLR was noticed in category 4 (28.92), and it was significant. On the other hand, in case of PLR highest mean was found in category 4 (525.86) only, followed by category 2 (186.20), category 3 (123) and category 1 (87.34). The difference was noticed to be significant. In case of CRP highest mean was in category 1 (49.75) followed by category 3 (48), category 2 (39.10) and category 4 (14). The difference was highly significant. For procalcitonin, highest mean was in category 3 (0.41) then category 2 (0.30), 1 (0.27) and 4 (0.24). The difference was again highly significant.

DISCUSSION

Acute exacerbation of COPD (AECOPD) is one of the major causes of mortality and morbidity with recurrent hospital admissions of COPD patients. There is need for discovering novel markers which can

determine the risk stratification in COPD patients so that appropriate management strategies can be framed.

Numerous studies have been done and many other studies are still underway which suggest that NLR, PLR, CRP and procalcitonin level in serum can significantly predict the exacerbation of COPD. CBC, which is commonly used in health facility, is a cheaper and easily accessible method which can be used to asses severity of COPD.

COPD involves pulmonary and systemic inflammatory process changes in innate immune system which results in alveolar damage, impaired phagocytosis and increased neutrophil marker which significantly leads to increased cytokine production followed by destruction of lung tissue.

In our study 50 cases of COPD were Included. These cases were both from OPD and IPD of Medicine Department of Guru Nanak Dev Hospital, GMC Amritsar. These cases were having exacerbations of the symptoms related to COPD were diagnosed by using various diagnostic criteria and were estimated for the correlation with NLR, PLR, Procalcitonin and CRP level.

These cases before registration into the study were explained about the study in their conversational language and an informed consent was taken for the same. In this study we enrolled 31 male and 19 females with all the cases having established diagnosis of COPD.

The mean age of the study participants was 51.4 years with the majority of the participants were within the age ranges of 41-50 years and 61-70 years, constituting 36% and 18% respectively. The gender distribution showed a slight male (62%) predominance over females (38%).

When GOLD category was analyzed it was found that majority of patients (58%) fell under GOLD category 2 followed by GOLD category 3 (22%), GOLD category 1(16%) and GOLD category 4(4%).

Upon analysis it was found that 62% patient were smokers.

Majority of the patients presented with breathlessness (92%) followed by cough (14%).

Procalcitonin in acute exacerbation of COPD

In our study, procalcitonin levels were higher in category 3 with mean of (0.41), Category 2 (0.30), Category 1 (0.27) and at Category 4 (0.24). The difference was highly significant in the study.

Pandey S et al in 2019 studied the procalcitonin level in serum of patients with AECOPD and compared with stable patients of COPD. Results showed that there was significant increase in mean serum procalcitonin levels in AECOPD group (1.31+/-0.79) as compared to stable group (0.1+/-0.09).

CRP in acute exacerbation of COPD

In our study, CRP was highest in GOLD category 1 with mean of (49.75) followed by category 3 (48), category 2 (39.1) and category 4

(14) .Difference was highly significant in our study.

Zoir HM et al.,in 2019 investigated difference in CRP levels between patients having AECOPD and with stable COPD patients, they also compared with 10 healthy controls. Results showed that there is significantly increased level of CRP in COPD patient as compared to healthy controls (p value <0.0001). Also AECOPD p value showed significantly increase CRP levels then those with stable COPD (p value<0.0001).

Arora s et al in 2019 investigated correlation between CRP and leptin with severity of COPD and nutritional status .102 COPD patients were correlated according to GOLD guidelines in which result showed that patients who were categorized as severe COPD having higher levels of CRP, along with poor nutritional status.

NLR In acute exacerbation of COPD

In our study it is seen that exacerbated COPD patients had significantly higher NLR values which shows that systemic inflammation is present in these patients.

This observation is consistent with other published data. In present study NLR also shows positive correlation with other markers such as CRP, procalcitonin and PLR. This also shows that potential use of NLR as inflammatory marker in prediction of exacerbation of COPD is valuable.

When parameters are analyzed against GOLD category it was found that highest mean in NLR was noticed in category 4 (28.20) which is significant. Overall mean was 13.80 with p value (0.043) which is significant.

Descriptive analysis showed that mean value of FEV1 was 59.80+/-

10.16 while other parameters were as follows FEV1/FVC 67.48+/- 1.70,Hb 11.7+/- 2.70, Neutrophils 82.44+/-8.91 lymphocyte 12.32+/- 7.53.

Kurkipek et al concluded cross sectional study in 2015 In a hospital of Turkey in dec 2012 to 2013 .Results revealed that there was significant increased mean value of CRP, NLR and PLR in AECOPD. NLR=3.3, PLR=150, CRP=5mg/dl and positive predictive value were 85%, 73%, 82% respectively which indicated NLR as parameter with higher prognostic value.

Thomson M et al in 2013 concluded prospective cohort study on 6574 patients which revealed elevated

biomarkers such as CRP, leucocyte
count and fibrinogen. Multivariate adjusted odds ratio and hazard ratio showed significant increase in levels of these biomarkers highlighting the relevance of these biomarkers in risk stratification for the management of COPD.

PLR in acute Exacerbation of COPD

For PLR highest mean was found in category 4 (525.80), category 2 (186.20), category 3 (123) and category 1 (87.34) difference was noticed to be significant. Overall mean was 170.06 with a standard deviation of 127.01 having p value (p 0.000).

Tugba C et al, in 2021 had done retrospective study analyzing the patients which were admitted to OPD clinic with established COPD He divided them in to 2 groups those having acute exacerbation (n=52) and those who were stable (n=64).NLR, MLR (Monocytes lymphocytes ratio)and PLR were calculated for both groups. Subjects were then divided based on NLR cutoff p value which were obtained by ROC curve (NLR<3.03 and NLR>3.03). Result showed significantly higher value of NLR, MLR (monocyte-lymphocyte ratio) and PLR in the exacerbation group (P<0.001).

Strength of the study design

Diagnosis was done with spirometry and CT scan of chest. The study needed only serum samples for the estimation of CRP levels along with CBC with differentials counts which was easier to get and checked.

Limitation of the study design

Study population consists of 50 cases only. Study was done over a period of 18 months. It was difficult to find out cases of COPD with exacerbation without comorbidities like superadded infection which also has an impact over the studied biomarkers. Procalcitonin is costly biomarker and cost is an issue in our country.

CONCLUSION

The study concluded that:-

1. Mean age of presentation of COPD was 51.40 and the majority of the patient lies between 41 to 70 years of age.
2. 62% male and 38 % were female patients.
3. Positive correlation established in between PLR and AECOPD
4. Positive correlation established between CRP level and AECOPD
5. Positive correlation established between procalcitonin level and AECOPD
6. Positive correlation established between NLR level and AECOPD.

Inflammatory biomarkers do have a role in predicting the risk stratification in AECOPD.

Its might help in planning and executing the management plan better suited for the subgroups which can result in better management of AECOPD patients

Hence improving the disease outcome and also providing improving quality of life for the patients of COPD.

BIBLIOGRAPHY

1. Chronic Obstructive Pulmonary Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease(2020report); 2020.
2. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest. 2009;135:975– 982.
3. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. Thorax. 2019;74:337–345.
4. Martinez FJ, Han MK, Flaherty K, Curtis J. Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. Expert Rev Anti Infect Ther. 2006;4:101–124.
5. Jindal SK, Aggarwal AN, Chaudhary K, Chhabra SK, D'Souza GA, Gupta D. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci. 2006;48(1):23-29.
6. Bhardwaj M, Saini V, Kaur J. Evaluation and Correlation of Serum C-Reactive Protein and Procalcitonin Levels in Acute Exacerbation and Stable Phase of Chronic Obstructive Pulmonary Disease Patients: An Observational Study. Journal of Clinical and Diagnostic Research. 2021;15(12):OC24-OC28.
7. Paliogiannis P, Fois AG, Sotgia S, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. Eur Respir Rev 2018; 27: 170113
8. Emami Ardestani M, Alavi Naeini N. Evaluation of the prognostic value of neutrophil-to-lymphocyte ratio and platelet-to- lymphocyte ratio in acute exacerbation of chronic obstructive pulmonary disease. J Res Med Sci. 2022 Jul 29;27:50.
9. Global Initiative for Chronic Obstructive Lung Disease. Global Initiative for Chronic Obstructive. GOLD, Glob Obstr Lung Dis. 2017;1-44.
10. Sethi S. Pathogenesis and treatment of acute exacerbations of chronic obstructive pulmonary disease. Semin Respir Crit Care Med. 2005;26:192–203.

11. Hirschmann JV. Do bacteria cause exacerbations of COPD? Chest. 2000;118:193–203.
12. Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1992;146:1067–1083.
13. Monsó E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, Ausina
14. V. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med. 1995;152:1316–1320.
15. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. N Engl J Med. 1969;280:397–404.
16. Sohy C, Pilette C, Niederman MS, Sibille Y. Acute exacerbation of chronic obstructive pulmonary disease and antibiotics: What studies are still needed? Eur Respir J. 2002;19:966–975.
17. Gao D, Chen X, Wu H, Wei H, Wu J. The levels of serum pro- calcitonin and high-sensitivity C-reactive protein in the early diagnosis of chronic obstructive pulmonary disease during acute exacerbation. Exp Ther Med. 2017 Jul;14(1):193-198.
18. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54(7):581-
19. 2.
20. Moody L, McCormick K, Williams A. Disease and symptom severity, functional status, and quality of life in chronic bronchitis and emphysema (CBE). J Behav Med 1990;13(3):297-306.
21. Schlecht NF, Schwartzman K, Bourbeau J. Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. Chron Respir Dis 2005; 2(4):183-91.
22. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(5 Pt 1):1418-22.
23. Garrod R, Marshall J, Barley E, Fredericks S, Hagan G. The relationship between inflammatory markers and disability in chronic obstructive pulmonary disease (COPD). Prim Care Respir J. 2007 Aug;16(4):236-40.
24. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65.
25. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology. 2011;11:445–52.
26. Sargin G, Senturk T, Yavasoglu I, Kose R. Relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio and disease
27. activity in rheumatoid arthritis treated with rituximab. Int J Rheum Dis. 2018;21:2122–7.
28. Ruta VM, Man AM, Alexescu TG, Motoc NS, Tarmure S, Ungur RA, Todea DA, Coste SC, Valean D, Pop MC. Neutrophil-To- Lymphocyte Ratio and Systemic Immune-Inflammation Index- Biomarkers in Interstitial Lung Disease. Medicina (Kaunas). 2020 Jul 29;56(8):381.
29. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. Ann Lab Med. 2019 Jul;39(4):345-357.
30. Bhowmik A, Seemungal TAR, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax. 2000;55:114–120.
31. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA. 2013 Jun 12;309(22):2353-61.
32. Kurtipek E, Bekci TT, Kesli R, Sami SS, Terzi Y. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease. J Pak Med Assoc. 2015 Dec;65(12):1283-7.
33. Kim YJ, Lim B, Kyung SY, Park JW, Jeong SH. Comorbidity and Inflammatory Markers May Contribute to Predict Mortality of High-Risk Patients With Chronic Obstructive Pulmonary Disease Exacerbation. J Clin Med Res. 2016;8(7):531-536.