Original Article

DOI: 10.7860/JCDR/2023/59293.17337

Neutrophil-Lymphocyte Ratio as a Predictor of COPD Exacerbations: A Cross-sectional Study

Internal Medicine Section

KARAN SHARMA[1], KRANTI GARG[2], JAWAHAR LAL JOSHI[3], VISHAL CHOPRA[4], RAMESH KUMAR KUNDAL[5]

ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is characterised by a modified inflammatory response to chronic irritants, which is often associated with some degree of systemic inflammation. Exacerbations in COPD are characterised by exaggeration of the ongoing inflammation. A number of inflammatory mediators are found to be raised in COPD exacerbations, but most of them are expensive and not readily available. The Neutrophil-lymphocyte Ratio (NLR) is a rapid, easy and cheap biomarker, that has been shown to be raised in patients of COPD.

Aim: To evaluate the role of NLR in patients of stable and acute exacerbation of COPD.

Materials and Methods: This cross-sectional observational study was conducted in Department of Pulmonary Medicine at Government Medical College, Patiala, Punjab, India. Study included 150 patients of stable COPD, 150 patients of Acute Exacerbation COPD (AECOPD) and 100 subjects as controls. NLR was calculated from a peripheral blood sample of the study participants. Continuous variables were summarised as mean with standard deviation and compared between groups using Unpaired t-test. A p-value <0.05 was considered statistically significant.

Results: The mean age in AECOPD group was 61.7±10.4 years, in stable COPD group was 63.1±8.9 years and 63.2±7.8 years in controls. Mean NLR was found to be highest in AECOPD group (4.0±1.7) followed by stable COPD (2.9±0.8) and then control (1.8±0.4). NLR showed good predictive value for predicting exacerbations in stable COPD patients with sensitivity and specificity of 75.3% and 70.7%, respectively (cut-off=3.4 and AUC=0.806).

Conclusion: The NLR is an easily available biomarker of inflammation and can be used as a predictor of exacerbation in patients of COPD.

Keywords: Biomarker, Chronic obstructive pulmonary disease, Inflammation

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterised by a modified inflammatory response to chronic irritants. There is an increase in the number of macrophages, activated neutrophils, and lymphocytes in peripheral airways, lung parenchyma, and vessels [1]. The role of the neutrophils in the pathogenesis of COPD is only partially known. The imbalance between proteases and their inhibitors cause parenchymal destruction and emphysematous changes, while the production of cytokines, enzymes, adhesion molecules, and growth factors from activated neutrophils promote infiltration of the airways by inflammatory cells and further production of proinflammatory factors, creating a vicious circle, which maintains and enhances the local and systemic effects of the disease [2,3].

Along with pulmonary inflammation, some degree of systemic inflammation is also seen in COPD, although the mechanism of this systemic inflammation remains unclear. Several pathways have been suggested that may lead to systemic inflammation in COPD, these include; overflow of inflammatory mediators from pulmonary compartment; proinflammatory reaction to bacterial products; inflammatory reaction to tissue hypoxia, and inflammation induced due to smoking [4]. During exacerbations of COPD, pulmonary as well as systemic inflammation is accentuated characterised by cellular activation, cytokine production and tissue injury. The infective (bacterial or viral [5]) and non infective triggers of exacerbations accentuate the ongoing inflammation in patients of COPD [6].

Increased inflammation in lungs is associated with raised inflammatory markers in circulation leading to an increase in systemic inflammation as well [4]. Several biomarkers of inflammation which are found to be raised in COPD are C-Reactive Protein (CRP), Interleukin-8 (IL-8), Tumour Necrosis Factor (TNF-α), leptin, endothelin-1, fibrinogen, IL-6, Leukotriene (LT) B4 and E4 [7]. Although some of these novel biomarkers can identify the severity of disease and acute exacerbation in COPD, most of them are time-consuming, expensive, and not readily available [8]. The Neutrophil-Lymphocyte Ratio (NLR) is a rapid, easy and cheap biomarker that is calculated from Complete Blood Count (CBC). Blood NLR has been demonstrated to be an indicator of inflammatory states and is utilised for risk stratification of several disorders, including acute coronary syndrome [9], pancreatitis [10], sepsis, and infectious conditions [11]. NLR is also been used as a prognostic indicator in several diseases like breast cancer [12], sepsis [13], and most recently in Coronavirus Disease 2019 (COVID-19) [14].

There has been extensive research on the role of NLR in COPD. Multiple studies have corroborated that NLR increases during exacerbations of COPD [8,15-24] and other studies have explored its role as a predictor of exacerbations [8,15,16,18,25,26] and mortality [17,24,25,27-30]. However, data in the Indian population is scarce. Prasannan G et al., and Sharma K et al., found that NLR was raised in COPD exacerbations when compared to stable patients [21,22]. Prasannan G et al., also found that NLR has a positive correlation with mMRC and BODE score of the patients [21]. While Arya V et al., found no correlation between NLR and severity of COPD exacerbation [31]. Hence, the present study was conducted to evaluate the role of NLR in patients of COPD, especially as a predictor of exacerbations.

MATERIALS AND METHODS

This cross-sectional observational study was conducted from June 2019 to November 2020, in Department of Pulmonary Medicine at Government Medical College, Patiala, Punjab, India. Institutional Ethical Committee approval was obtained for the study (BFUHS/2K19p-TH/2073).

Inclusion criteria: All patients attending the study Institute with diagnosis of COPD {as per GOLD 2018 report criteria [1]} were included in the study.

Exclusion criteria: Pregnant and lactating females, and patients with bronchiectasis, active tuberculosis, malignancy, or other inflammatory diseases such as arthritis, inflammatory bowel diseases, or connective tissue disorders were excluded from the study.

Patients of COPD were divided into two groups of 150 patients each.

COPD group (n=150): One group was of stable patients of COPD, defined as those with no significant change in symptoms and no need for additional therapy for the past three months [32].

AECOPD group (n=150): All patients with Acute Exacerbation of COPD (AECOPD) which was defined as an acute worsening of symptoms in COPD patient that requires additional therapy [1].

Controls (n=100): Healthy subjects with no history of smoking or biomass exposure, no co-morbidities, and no clinical symptoms.

Data Collection

Baseline demographic data and clinical history was noted. Blood samples were collected from participants and subjected to total and differential leucocyte count, absolute eosinophil and neutrophil counts. Neutrophil-lymphocyte ratio was calculated by dividing neutrophil count with lymphocyte counts.

STATISTICAL ANALYSIS

Categorical variables were summarised as proportions. Continuous variables were summarised as mean with Standard Deviation (SD) and compared between groups using Unpaired t-test. A p-value <0.05 was considered statistically significant. Data was analysed using R software version 4.0.1.

RESULTS

The mean age in AECOPD group was 61.7±10.4 years, in stable COPD group was 63.1±8.9 years and 63.2±7.8 years in controls. Male predominance was seen in all three groups studied. The mean BMI of participants was significantly lower in stable COPD patients, as compared to AECOPD and controls. Only 82% patients of AECOPD and 77.3% of stable COPD patients were smokers, biomass fuel exposure was present in 23.3% and 26.7% of patients of AECOPD and stable COPD respectively. Current smokers were significantly higher in AECOPD group, as compared to stable COPD group [Table/Fig-1].

Variables		AECOPD (n=150)	Stable COPD (n=150)	Controls (n=100)	p-value
Age years (mean±SD)		61.7±10.4	63.1±8.9	63.2±7.8	0.34
Body Mass Index (kg/m^2) (mean±SD)		21.8±3.6	22.5±3.2	21.4±3.0	0.03
Gender	Female	29 (19.3%)	35 (23.3%)	22 (22%)	0.69
	Male	121 (80.7%)	115 (76.7%)	78 (78%)	
Smoking history	Current	43 (35%)	14 (12.1%)	0	<0.001
	Ex-smoker	80 (65%)	102 (87.9%)	0	
Biomass exposure		35 (23.3%)	40 (26.7%)	0	0.50

[Table/Fig-1]: Clinicodemographic characteristics of study participants.

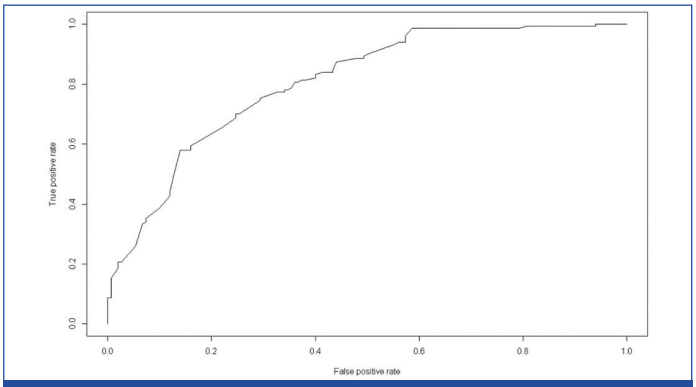
When comparing haematological parameters between AECOPD and stable COPD groups, total leucocyte count, neutrophil percentage, absolute neutrophil count, and absolute eosinophil count were significantly higher in the AECOPD group compared to stable COPD group. Mean NLR was significantly higher in AECOPD group (4.0±1.7) compared to stable COPD group (2.9±0.8). However, there was no significant difference in haemoglobin levels or eosinophil percentage between the two groups.

Comparative evaluation of haematological parameters between stable COPD patients and controls showed that the total leucocyte count, neutrophil and eosinophil percentage, and absolute eosinophil and neutrophil counts were significantly lower in control group compared to stable COPD group. The mean NLR was significantly higher in stable COPD group compared to control group. Comparison of haematological parameters between AECOPD and controls revealed that the total leucocyte count, neutrophil and eosinophil percentage, absolute eosinophil count, and absolute neutrophil count were significantly higher in the AECOPD patients, compared to controls group. NLR was significantly higher in AECOPD group compared to control group [Table/Fig-2].

Haematological parameter	AECOPD group (mean±SD)	COPD group (mean±SD)	Controls group (mean±SD)	p-value
Haemoglobin (g/dL)	10.6 (1.8)	10.8 (2.2)	10.4 (2.1)	0.30* 0.22# 0.69^
Total leucocyte count (per µL)	13044.0 (1699.5)	9985.3 (1489.1)	8974.0 (1718.3)	<0.001*#^
Neutrophils (%)	75.1 (4.1)	69.4 (5.7)	61.6 (4.4)	<0.001*#^
Lymphocytes (%)	20.0 (4.2)	25.6 (5.2)	34.8 (4.1)	<0.001*#^
Eosinophils (%)	3.4 (0.8)	3.4 (1.4)	2.2 (1.3)	0.84* <0.001#^
Absolute eosinophil count (per µL)	444.3 (137.1)	334.7 (148.3)	197.0 (134.9)	<0.001*#^
Absolute neutrophil count (per µL)	9839.9 (1710.5)	6918.1 (1120.6)	5507.7 (1012.4)	<0.001*#^
NLR	4.0±1.7	2.9±0.8	1.8±0.4	<0.001*#^

[Table/Fig-2]: Haematological parameters and NLR among study participants. *AECOPD vs Stable, #Stable vs Controls, ^AECOPD vs Controls

Receiver-Operating Characteristic (ROC) analysis revealed a good predictive value of NLR for predicting an exacerbation of COPD. At a cut-off of 3.4, the sensitivity, specificity and Area Under Curve (AUC) were 75.3%, 70.7% and 0.806, respectively [Table/Fig-3].



[Table/Fig-3]: Receiver-operating characteristic curve of NLR for prediction of exacerbation in patients of COPD.

Study participants were characterised, based on blood eosinophil percentage into two groups i.e., blood eosinophils <2% and ≥2%. In patients of AECOPD, NLR was found to be significantly higher in non eosinophilic group (blood eosinophils <2%) and in those, with blood eosinophils ≥2%. NLR was similar in two groups in patients of stable COPD and controls [Table/Fig-4].

Variables	Eosinophil <2%	Eosinophil ≥2%	p-value
Normal subjects	(n=44)	(n=56)	
NLR	1.8 (0.4)	1.8 (0.5)	0.73
Acute exacerbation patients	(n=3)	(n=147)	
NLR	7.7 (6.8)	4.0 (1.4)	<0.001
Stable COPD patients	(n=7)	(n=143)	
NLR	2.4 (0.8)	2.9 (0.8)	0.12

[Table/Fig-4]: NLR in non eosinophilic (blood eosinophils <2%) and eosinophilic (blood eosinophils ≥2%) groups among study participants.

DISCUSSION

In the present study, the Total Leucocyte Counts (TLC) in patients of stable COPD were significantly higher than controls, a finding that was present consistently in previous studies [8,15,19,20,24]. COPD is characterised by an altered inflammatory response to airway irritants leading to parenchymal and airway destruction which further causes persistent symptoms and airflow limitation. Apart from airway inflammation, an abnormal systemic inflammation is also seen in COPD, which in turn is responsible for most of the systemic manifestations of the disease. Several mechanisms have been proposed in order to explain systemic inflammation in COPD, like systemic spread of inflammatory mediators from pulmonary compartment, an inflammatory response to tissue hypoxia or bacterial components, smoking induced inflammation, pulmonary hyperinflation [4]. Furthermore, exacerbation of COPD is characterised by increased inflammation as a result of infective aetiology in most cases and hence, leads to higher TLC, which is seen in the present study, as well as, in previous literature [8,15,19,20,24], when compared to controls or stable COPD patients.

In the present study, it was found that NLR was significantly higher in stable COPD, when compared to controls and even higher in AECOPD when compared to stable COPD and controls. Similar findings have been reported by a number of studies [Table/Fig-4]. NLR is an established marker of inflammation and has been shown to increase in several inflammatory conditions [9-14]. Exacerbations in COPD are characterised by flaring of the chronic inflammatory process of COPD at pulmonary and systemic level. Bacterial, viral as well as non infectious causes of exacerbations lead to increased inflammation in airways and release of proinflammatory cytokines and chemokines [6]. These markers of inflammations are often increased in AECOPD and lead to heightened systemic inflammation in form of neutrophil recruitment and activation. These result in a higher NLR in AECOPD, when compared to stable COPD and controls.

Since, NLR is significantly higher in AECOPD, it could be used as a biomarker of exacerbation in patients of COPD. In the present study a cut-off value of 3.4 showed a sensitivity and specificity of 75.3%, and 70.7%, for predicting an exacerbation. Several previous studies have also found a good predictive value of NLR in predicting an exacerbation of COPD [Table/Fig-5] [8,15,17,18,20-24,26].

Studies	AECOPD	Stable COPD	Controls	p-value
NLR (Mean±SD)				
Current study	4.0±1.7	2.9±0.8	1.8±0.4	<0.001
Yousef AM and Alkhiary W [15]	4.44	2.36	1.45	<0.001
Xiong W et al., [17]	-	4.88±1.84	2.02±1.92	<0.001
Taylan M et al., [8]	7.1±0.9	3.1±2.5	1.7±0.9	<0.001
Mohamed-Hussein AA et al., [24]	3.7±0.3	1.2±0.7	-	<0.05
Şahin F et al., [20]	8.51±8.70	2.79±1.65	1.31±0.46	<0.001
Prasannan G et al., [21]	5.523	4.226	-	0.008
Sharma K et al., [22]	6.389±3.071	4.263±1.900	-	0.0009
El-Gazzar AG et al., [23]	2.65 ±0.41	2.24±0.56	-	<0.0001
NLR cut-off for predicting exacerbations	**Cut-off**	**Sensitivity**	**Specificity**	**AUC (95% CI)**
Current study	3.4	75.3%	70.7%	0.806
Yousef AM and Alkhiary W [15]	3.12	86.7%	76.7%	0.878
Taylan M et al., [8]	3.29	80.8%	77.7%	0.894
Farah R et al., [18]	7.30	76.80%	73.10%	0.79
Acartürk Tunçay E et al., [26]	3.54	78%	69%	-

[Table/Fig-5]: Summary of findings in the current study and previous similar studies [8,15,17,18,20-24,26].

A significantly higher NLR was found in patients of AECOPD with blood eosinophil percentage <2%, when compared to those with eosinophils ≥2% but no significant difference was found when categorising controls and stable COPD patients into these categories. Moreover, the number of AECOPD patients showing this trend was very less, hence, no conclusion could be drawn from this finding.

Limitation(s)

The NLR was not evaluated with respect to other variables like severity of underlying COPD, severity of exacerbations, frequency of previous exacerbations. Since, it was a cross-sectional study and no follow-up was done, prognostic role of NLR was not studied.

CONCLUSION(S)

Frequent and severe exacerbations of COPD adversely affect the health status of the patient and also, contribute to progression of disease and mortality [1]. Predicting exacerbations early can help in early detection and management. Current study shows that, NLR is an inflammatory biomarker that raises significantly during COPD exacerbations and can be used to predict COPD exacerbations, and help in detecting exacerbations early.

REFERENCES

[1] Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease, 2018 report. Glob Initiat Chronic Obstr Lung Dis. 2018;4. [cited 2021 Jan 15]. Available from: www.goldcopd.org.
[2] Barbu C, Iordache M, Man MG. Inflammation in COPD: Pathogenesis, local and systemic effects. Rom J Morphol Embryol. 2011;52:21-27.
[3] Hoenderdos K, Condliffe A. The neutrophil in chronic obstructive pulmonary disease: Too little, too late or too much, too soon? Am J Respir Cell Mol Biol. 2013;48:531-39.
[4] Wouters E. Local and systemic inflammation in chronic obstructive pulmonary disease. Proc Am Thorac. Soc. 2005;2:26-33.
[5] Mallia P, Johnston SL. How viral infections cause exacerbation of airway diseases. Chest. 2006;130:1203-10.
[6] Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J. 2007;29:1224-38.
[7] Hurst JR, Donaldson GC, Perera WR, Wilkinson TMAA, Bilello JA, Hagan GW, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;174:867-74.
[8] Taylan M, Demir M, Kaya H, Selimoglu Sen H, Abakay O, Carkanat AI, et al. Alterations of the neutrophil-lymphocyte ratio during the period of stable and acute exacerbation of chronic obstructive pulmonary disease patients. Clin Respir J. 2017;11:311-17.
[9] Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102:653-57.
[10] 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.
[11] Yoon NB, Son C, Um SJ. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Ann Lab Med. 2013;33:105-10.
[12] Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: A systematic review and meta-analysis. Breast Cancer Res. 2017;19:2.
[13] Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. Am J Emerg Med. 2020;38:641-47.
[14] Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020;92:1733-44.
[15] Yousef AM, Alkhiary W. Role of neutrophil to lymphocyte ratio in prediction of acute exacerbation of chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc. 2017;66:43-48.
[16] Pascual-González Y, López-Sánchez M, Dorca J, Santos S. Defining the role of neutrophil-to-lymphocyte ratio in COPD: A systematic literature review. Int J Chron Obstruct Pulmon Dis. 2018;13:3651-62.
[17] Xiong W, Xu M, Zhao Y, Wu X, Pudasaini B, Liu JM, et al. Can we predict the prognosis of COPD with a routine blood test? Int J COPD. 2017;12:615-25.
[18] Farah R, Ibrahim R, Nassar M, Najib D, Zivony Y, Eshel E, et al. The neutrophil/lymphocyte ratio is a better addition to C-reactive protein than CD64 index as a marker for infection in COPD. Panminerva Med. 2017;59:203-09.
[19] Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinellu E, Pirina P, et al. The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: A systematic review and meta-analysis. Eur J Clin Invest. 2018;48:0-2.
[20] Şahin F, Koşar AF, Aslan AF, Yiğitbaş B, Uslu B. Serum biomarkers in patients with stable and acute exacerbation of chronic obstructive pulmonary disease: A comparative study. J Med Biochem. 2019;38:503-11.

[21] Prasannan G, Muralidharan K, Premkumar VT. Neutrophil-lymphocyte ratio as a marker of disease severity and exacerbation in COPD. Indian J Appl Res. 2019;9:17-20.
[22] Sharma K, Singh G, Singh U. To compare neutrophil lymphocyte ratio with other parameters in acute exacerbation of COPD and stable COPD: A hospital based study. Asian J Med Res. 2020;9:PM20-23.
[23] El-Gazzar AG, Kamel MH, Elbahnasy OKM, El-Naggar MES. Prognostic value of platelet and neutrophil to lymphocyte ratio in COPD patients. Expert Rev Respir Med. 2020;14:111-16.
[24] Mohamed-Hussein AAR, Aly SS, Zahran AM, Sadek SH. Neutrophil CD64 and Neutrophil/Lymphocyte ratio as predictors of hospital outcome in acute exacerbation COPD. Int J Adv Sci Res Manag. 2017;2(7):07-17.
[25] Ye Z, Ai X, Liao Z, You C, Cheng Y. The prognostic values of neutrophil to lymphocyte ratio for outcomes in chronic obstructive pulmonary disease. Medicine (Baltimore). 2019;98:e16371.
[26] Acartürk Tunçay E, Karakurt Z, Aksoy E, Saltürk C, Gungor S, Ciftaslan N, et al. Eosinophilic and non-eosinophilic COPD patients with chronic respiratory failure: Neutrophil-to-lymphocyte ratio as an exacerbation marker. Int J COPD 2017;12:3361-70.
[27] Kumar P, Law S, Sriram KB. Evaluation of platelet lymphocyte ratio and 90-day mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. J Thorac Dis. 2017;9:1509-16.
[28] Teng F, Ye H, Xue T. Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease. PLoS One. 2018;13:e0204377.
[29] Liu J, Liu J, Zou Y. Relationship between neutrophil-lymphocyte ratio and short-term prognosis in the chronic obstructive pulmonary patients with acute exacerbation. Biosci Rep. 2019;39:20190675.
[30] Emami Ardestani M, Alavi Naeini N. Evaluation of the relationship of neutrophil-to lymphocyte ratio and platelet to lymphocyte ratio with in-hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. Clin Respir J. 2021;15:382-88.
[31] Arya V, Gupta A, Malhotra AK. Correlation of neutrophil lymphocyte ratio with the severity of chronic obstructive pulmonary disease: A cross-sectional study. Int J Heal Clin Res. 2020;3:90-95.
[32] Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932-46.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.
2. Associate Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.
3. Associate Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.
4. Professor and Head, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.
5. Professor and Head, Department of Pathology, Government Medical College, Patiala, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kranti Garg,
Associate Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.
E-mail: drkrantigarg@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 28, 2022
- Manual Googling: Oct 26, 2022
- iThenticate Software: Nov 02, 2022 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 26, 2022**
Date of Peer Review: **Oct 06, 2022**
Date of Acceptance: **Nov 03, 2022**
Date of Publishing: **Jan 01, 2023**