Chest Heart Journal
Vol. 43, No. 2, July 2019

ORIGINAL ARTICLE

Association between Platelet Indices and the Severity of Acute Exacerbation of COPD

Mahmuda Begum[1], Snehashis Nag[2], Md. Sayedul Islam[3], Sanjoy Kumar Kar[4], Subrata Kumar Gain[4]

Abstract

Background: *Chronic obstructive pulmonary disease (COPD) is the most commonly encountered respiratory problem in hospital setting which leads to disability and even death. Recent studies have shown that the platelet indices are associated with several cardiovascular diseases including COPD. There is little data on COPD and its relation with platelet indices and more limited data is observed regarding the relationship between platelet indices and the severity acute exacerbation of COPD.*

Objective: *To find out the association between platelet indices and severity of acute exacerbation of COPD*

Methods*: This cross-sectional observational study was conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) for July 2018 to June 2019. The study adhered with the declaration of Helsinki and all ethical measures were taken properly throughout the study. All adult patients with COPD admitted during the study period were approached and included into the study. Before final selection, informed consent was taken from all participants. All patients were subjected to detailed history taking, physical examination and relevant examination especially a complete blood count. Total 100 patients were interviewed with a preformed and pretested questionnaire. Following completion of the data collection, all data were inputted into the statistical software. Final analysis was done with the help of SPSS 20.*

Results: *Among the 100 study participants, mean age was 61.94±10.30 years (age range: 42 to 85 years). Male-female ratio was 2.70:1 (73% vs 27%). About 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity of COPD during admission. Platelet count was similar across the severity of the patients ($p>0.05$) but PLR, MPV, PDW and Plateletcrit increased significantly with increasing severity of COPD ($p<0.05$ all). According to the clinical assessment, 48% patients had acute respiratory failure non-life-threatening condition, 28% had no respiratory failure and 24% of them presented with life-threatening acute respiratory failure. Further analysis suggests that PLR, MPV, and PDW increased significantly with increasing severity of exacerbations ($p<0.05$ all). But TPC, PLR and Plateletcrit are not significantly related with severity of COPD exacerbation.*

Conclusion: *Platelet indices (MPV, PDW, Pct, PLR) change with severity of exacerbation of COPD patients and with severity of COPD (worsening of FEV_1) and can assess the severity of these conditions.*

[Chest Heart J. 2019; 43(2) : 84-92]
DOI: http://dx.doi.org/10.33316/chab.j.v43i2.2019606

Introduction:

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

1. Junior Consultant, Medicine, National Institute of Neurosciences, Hospital, Shere Bangla Nagar, Agargoan, Dhaka-1207.
2. Registrar, Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212.
3. Associate Professor, Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212.
4. Registrar, Respiratory Medicine, NIDCH, Mohakhali, Dhaka

Correspondence to: Dr. Md. Sayedul Islam, Associate Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka-1212, Mob: 01552-390582, E-mail: drsayedul@gmail.com

Submission on: 1 July, 2019 **Accepted for Publication:** 5 July, 2019
Available at http.//www.chabjournal.org

caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. These changes do not always occur together, but evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow limitation and mucociliary dysfunction is a characteristic feature of the disease. Airflow limitation is usually measured by spirometry as this is the most widely available and reproducible test of lung function[1].

COPD is currently the fourth leading cause of death in the world (Lozano, Naghavi, Foremen[2] but is projected to be the 3rd leading cause of death by 2020. COPD represents important public health challenge. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and increasing age of the population[3].

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy[4]. These are complx events usually associated with increased airway inflammation,increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the main sympom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze.

Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission and disease progression. Hospitalizaion for an exacerbation is associated with poor prognosis and increased risk of death.

Inspite of such alarming outtcomes, very less data are available regarding the precipitating factors and predictors of prognosis in patient with acute exacerbation of COPD especially from developing countries[5] .

COPD is identified mainly post bronchodilator forced expiratory volume in 1st second (FEV1) / forced vital capacity ratio less than 0.7; severity determined by FEV1 alone combined with a history of exposure to risk factors. (GOLD 2019). In mild and moderate group there is considerable evidence of under diagnosis. Due to heterogenic presentation and lack of available diagnostic tests, acute exacerbation of COPD (AECOPD), are often diagnosed based on clinical gestalt, which is subjective and variable within and across physicans.

Therefore there is clearly a need for a biomarker or simple diagnostic tool that can aid with the diagnosis, risk stratification and assessment of therapeutic iterventions. It an provide an insight in the pathophysiological mechanism in exacerbation of COPD[6].

According to several studies, platelet and their indices may be used as inflammatory markers for cardiovascular, inflammatory and thromboembolic diseases[7]. The parameters related to platelet size reflect platelet activity and termed as platelet indices. These include the mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT)[8]. Previous studies have shown that high MPV, PDW and PCT are associated with increased inflammatory state in the body, as well as with the severity and acute exacerbation of COPD. Platelet interact with the leukocytes and secrete a number of mediators that are involved in immune modulation. Therefore, novel platelet indices reflecting platelet activity may provide information on the inflammatory status on certain diseases. The lymphocyte count in peripheral blood has been shown to inversely correlate with inflammation. The platelet –to-lymphocyte ratio (PLR) is an index to calculated through dividing platelet count by lymphocyte count in the peripheral blood[9]. It was on this background that the present study was conducted, which was aimed to investigate the association between platelet parameters including the MPV, PDW, PCT, PLR with the severity of acute exacerbation of COPD.

Objectives of the Study

General Objective:

- To find out any association between platelet indices and severity of acute exacerbation of COPD.

Specific Objectives:

- To find out relationship between Platelet Distribution Width (PDW) and acute exacerbation of COPD.
- To find out relationship between Mean Platelet Volume (MPV) and acute exacerbation of COPD.
- To find out relationship between plateletcrit and acute exacerbation of COPD.
- To find out any relationship between Platelet-Lymphocyte Ratio and acute exacerbation of COPD

Materials and methods

Study design: Cross sectional observational study

Study place: Respiratory Medicine Department of NIDCH

Study period: July 2018 – June 2019

Study population: COPD Patients admitted in NIDCH.

Inclusion criteria: Patients admitted with acute exacerbation of COPD.

Exclusion criteria:

Age less than 40 years, COPD patients with following diseases: Ischaemic heart disease, ACO, Active PTB/ Pneumonia, Cardiac failure, Renal Disease, Thromboembolic disorder, Carcinoma, Inflammatory bowel disease, Hepatic failure, Patient with antiplatelet medication, Recent blood transfusion, Unwilling to take part in study.

Study Procedure:

- Data were collected by following procedure:
- Before starting the study, the study was ethically permitted by ERB of NIDCH.
- Total 145 adult patients with shortness of breath who were admitted in NIDCH within study period were approached, after few days when they were stable to perform spirometry, spirometry with reversibility were done. 45 patients were excluded as asthma and ACO. Data of 100 patients was included in this study.
- After admission the patients were clinically assessed by duty doctor and then by researcher. Following that, chest x-ray, ABG and other relevant investigations were sent.
- After describing the purpose and objective of the study, written Informed consent was obtained from the patients.
- Data were collected by face to face interview by using a semi-structured questionnaire containing socio-demographic parameters and clinical presentations of COPD. Risk factor profiles and data on respiratory system findings were noted properly.
- All patients were subjected to perform blood test especially for CBC following admission. Blood samples were obtained before medication. Samples were collected in EDTA-containing and anticoagulant-free tubes.
- After immediate centrifugation for 10 minutes, at 4 °C, plasma and serum samples were separated in Eppendorf tubes and frozen immediately at -80 °C until analysis. Complete blood count parameters [including platelet (PLT) ($\times 10^5$/¼L), MPV (fL), PDW (fL), platelet lymphocyte cell ratio (P-LCR) (%), plateletcrit (PCT) (%)] were obtained with automatic hematology analyzer (Siemens-Sysmex, Germany).
- Few days after admission Spirometry was performed and COPD patients were diagnosed based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD), they were classified into four groups on basis of airflow limitation severity, according to the guideline based on post bronchodilator forced expiratory volume in one second (FEV1).
- Patients with acute exacerbation of COPD sub-divided into 3 classes: a) No respiratory failure; b) Acute respiratory failure non-life threatening, c) Life threatening acute respiratory failure.
- All collected data were noted into case record form.
- Data were verified and summarized.

Tabulation, Graphical presentation and analysis were done by SPSS (version 25.0.0.0) and Epi (version 7.1.5.0) info software.

Data processing and analysis:

After collection of all required data were checked, verified for consistency and then tabulated into the computer using the Microsoft excel 2016 software. SPSS (Statistical Package for Social Sciences) for Windows 20.0 package program was used for

statistical evaluations. Statistical significance was set as 95% confidence level at 5% acceptable error level. Descriptive statistics were obtained, and data were tested for normality using the Kolmogorov-Smirnov test for Gaussian distribution. Patients' characteristics were reported as percentages in case of categorical variables whereas continuous variables were expressed with mean ± standard deviation. The relationship between the categorical variables of the groups was examined by chi-square test. For comparison of parameters with normal distribution, parametric tests and comparison of parameters with abnormal distribution, non-parametric tests were used. Relationships between variables were assessed with Pearson's or Spearman's correlation coefficient. A p value <0.05 was considered as statistically significant.

Observation & Results

Total 100 patients of COPD who were admitted with acute exacerbations were included in the study. The

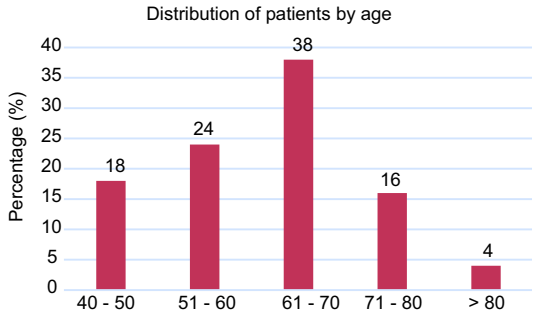

Fig.-1: *Distribution of patients by age (n=100)*

mean age was 61.94±10.30 years, ranging from 42 to 85 years. Majority of the patients were aged between 61 – 70 years (38%). figure I.

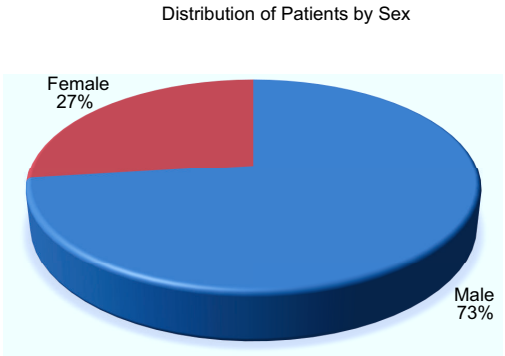

Fig.-2: *Distribution of patients by sex (n=100)*

Most of the patients were male (73%) and rest was females (27%). Male-female ratio was 2.70:1. (Figure 2)

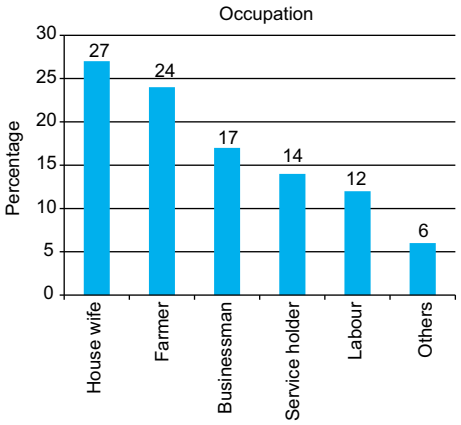

Fig.-3: *Distribution of patients by their occupation (n=100)*

Among all patients, 27% were housewives, 24% were famers, 17% were businessman, 14% were service holders, 12% were day labourer and 6% were doing other jobs. (Figure 3)

Table-I

Risk factors of study population (n=100)

Risk factors	Percent (%)
Smoking	68
Number of cigarettes smoked (pack year)	28.42±8.35*
Passive smoking	11
Biomass fuel use	17
Exposure to dust fumes at work place	21
Alcohol intake	4

* Mean±SD

Among all COPD patients, 68% percent patients were active smokers and 11% were passive smokers. Seventeen percent were using biomass fuel and 21% were exposed to work space dust/ fumes. Only 4% patients were alcohol users.

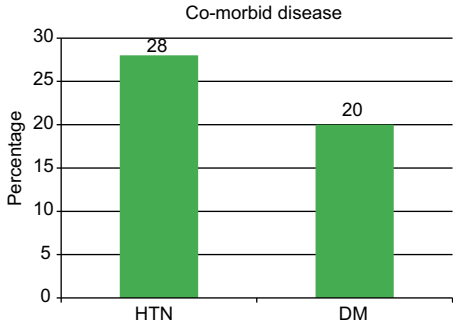

Fig.-4: *Distribution of patients according to presence of co-morbid disease (n=100)*

Among all twenty eight percent had HTN and twenty percent had DM. (Figure 4)

Table-II

Symptoms leading to hospitalization (n=100)

Symptoms	Percent (%)
Increased shortness of breath	84
Increased cough with sputum production	49
Cough with purulent sputum production	42
Fever	32
Bilateral leg swelling	32
Weakness and fatigue	83
Disorientation	48

The most common symptom leading to hospitalization in these patients was increasing shortness of breath (84%) followed in by weakness and fatigue (83%). Besides, 49% patients had increased cough with sputum production, 48% had disorientation, 42% cough with purulent sputum, 32% had fever, and 32% had bilateral leg swelling.

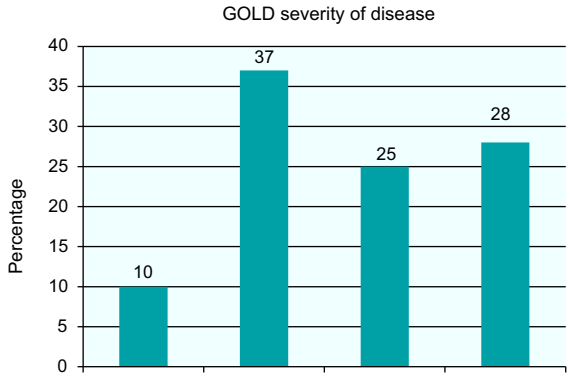

Fig.-5: *Distribution of patients according to their disease severity (n=100)*

Table-III

Previous history of exacerbations and hospitalization (n=100)

Variable	Percent (%)
Past history of Exacerbations	
None	23
One	26
Two	25
Three	15
Four	11
Past history of Hospitalization	
One	32
Two	8
Three	5

Majority 26% patients had one previous episodes of exacerbation and 32% patients had at least one previous history of hospitalization.

Severity was calculated using GOLD criteria. Among all 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity.

Total platelet count were increasing across severity groups ($p>0.05$). But lymphocyte count decreased with increasing severity ($p<0.05$). PLR, MPV, PDW and Plateletcrit increased significantly with increasing severity of CPD ($p<0.05$ all).

Among all 48% patients had acute respiratory failure non-life-threatening state, 28% had no respiratory failure and 24% of the patients had life threatening acute respiratory failure..

Table-IV

Platelet indices of patients in relation to severity of disease according to GOLD criteria (n=100)

Parameters	Severity of disease				P value
	Mild N = 10 Mean±SD	Moderate N = 37 Mean±SD	Severe N = 25 Mean±SD	Very Severe N = 28 Mean±SD	
Lymphocyte (/ml)	2552±1067	1920±1428	1862±1105	1340±564	0.027
Total platelet count (/ml)	244000±47628	240729±77392	2716000±77308	280321±77592	0.144
PLR	111±43.90	159.32±62.34	203.28±122.66	226.24±72.82	<0.001
MPV, fl	7.77±0.30	7.95±0.55	9.06±0.36	9.88±0.79	<0.001
PDW	13.34±0.50	14.30±1.36	15.81±0.99	17.47±1.41	<0.001
Plateletcrit, %	0.18±0.02	0.25±0.14	0.26±0.06	0.29±0.04	0.002

P value determined by ANOVA; PLR: Platelet lymphocyte ratio; MPV: mean platelet volume, PDW: Platelet distribution width

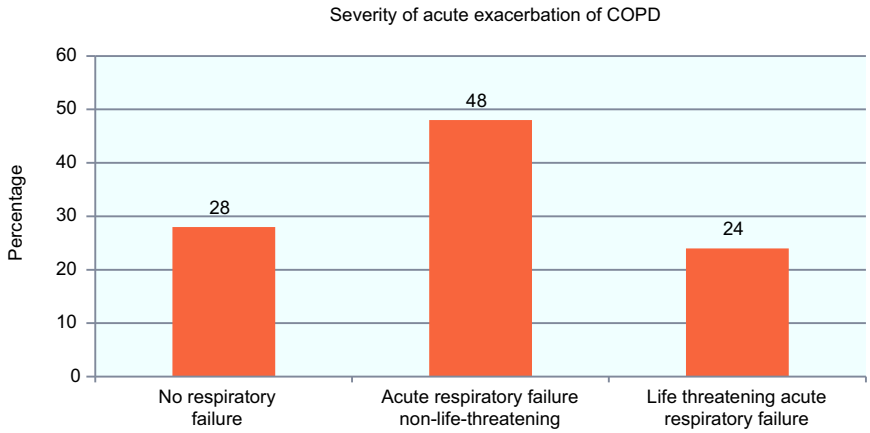

Fig.-6: *Distribution of patients according to clinical severity of acute exacerbation of COPD (n=100)*

Table-V

Platelet indices of patients in relation to severity of acute exacerbations of COPD (n=100)

Parameters	Severity of acute exacerbations			P value
	No respiratory failure N = 28 Mean±SD	Acute respiratory failure non-life-threatening N = 48 Mean±SD	Life threatening acute respiratory failure N = 24 Mean±SD	
Total platelet count (/ml)	250607±71536	257958±80719	274458±72582	0.520
PLR	169.34±97.37	177.80±83.61	214.39±88.96	0.255
MPV, fl	8.52±0.85	8.48±0.95	9.57±0.92	<0.001
PDW	14.93±1.86	15.28±1.74	16.47±1.92	0.008
Plateletcrit, %	0.23±0.06	0.25±0.11	0.28±0.09	0.263

P value determined by ANOVA; PLR: Platelet lymphocyte ratio; MPV: mean platelet volume, PDW: Platelet distribution width

PLR, MPV, and PDW increased significantly with increasing severity of exacerbations ($p<0.05$ all). TPC, PLR and Plateletcrit also increased with severity but was not significant.

Discussion:

A number of previous studies have shown that high MPV, PDW, and PCT are associated with increased inflammatory state in the body, as well as with the severity and acute exacerbation of COPD[10]. This study evaluated the platelet indices of COPD patients admitted with acute exacerbation and tested the association of platelet indices with COPD severity.

One hundred patients with acute exacerbation of COPD were included in this study. Mean age of the patients were 61.94±10.30 years ranging from 42 to 85 years. Approximately 2/3rd of the patients were aged above 60 years (58%). COPD is a disease of the old age. A study conducted by Alam and colleagues in both urban and rural settings of Bangladesh found a higher prevalence of COPD among older individuals[11]. In their study COPD prevalence was 27.5% among patients aged 60 – 69 years, 13.6% among patients aged 50 – 59 years and 5.2% among patients aged 40 – 49 years. A similar pattern was noted in among COPD patients in this study- 38% were aged 61 – 70 years, 24% were aged 51 – 60 years and 18% were aged 40 – 50 years.

Male patients were 2.70 times higher than the female patients constituting 73% of the study

population. Kabir et al noted that COPD prevalence is high among male patients(Kabir, Hasan and Rahman, 2016). This was also noted by Hossain and Karim who found 76.9% male and 23.1% female COPD patients in their study[12]. This can be explained by the fact that significantly more male are smokers in the Bangladesh than female (Demeo and Silverman, 2004). Worldwide a higher prevalence of COPD among male was also noted. Ntritsos et al. conducted a systematic review and meta-analysis to determined sex specific prevalence of COPD worldwide and found a summary prevalence of 9.23% in men and 6.16% in women[13].

In this study 58% patients came from rural area and 42% came from urban area. This is comparable with the findings of Alam et al who found a higher prevalence of COPD among rural participants.

The present study found that 40% patients had primary education and 20% were illiterate creating a bulk of lower educated individuals. On the other hand, 36% of the study population were manual workers (24% patients were farmers and 12% patients were labourers). COPD in these groups can be linked to the findings of Khandker et al. They found that 50% of the people with primary education were smokers and 66.75 of the manual workers were smokers in their study[14]. While in this study 68% patients were active smokers and 11% were passive smokers. A large of proportion of housewives was also noted with a history of exposure to biomass fuel.

Among all 45 were from middle class family and 39% were from lower class family. Only 16% were from upper class family. This may be due to improved hygienic practice in this higher class of people. Grigsby et al found that COPD prevalence is lower with higher monthly household income supporting picture of this study[15].

HTN was found in 28% patients and DM in 20% patients. Hypertension is one of the five most prevalent comorbidities among COPD patients which is responsible of hospitalization of these patients (Pavord *et al.*, 2016). DM is also an important co-morbidity found among hospitalized COPD patients .

The present study found that 77% patients had past history of one or more exacerbations and 45% patients had at least one past history of hospitalization. Bahadori and Fitzgerald ran a systematic study on the factors associate with recurrent exacerbations and admissions in the COPD patients[16] and found that three predictive factors: previous hospital admission, dyspnea and oral corticosteroids were all found to be significant risk factors of read- missions and variables including using long term oxygen therapy, having low health status or poor health related quality of life and not having routine physical activity were all associated with an increased risk of both admission and readmission to hospital. In the present study 84% patients were readmitted due to increasing shortness of breath, and 31% patients were using oral corticosteroid. Poor adherence to medication can be another cause for frequent readmissions.

Among 100 patients, 37% had moderate severity, 28% had very severe disease, 25% had severe disease and 10% had mild severity according to GOLD criteria. Among hematological parameters hemoglobin decreased significantly with increasing GOLD severity of COPD ($p<0.05$). WBC count and total platelet count was similar across severity groups ($p>0.05$). But lymphocyte count decreased with increasing severity ($p<0.05$). PLR, MPV, PDW and Plateletcrit increased significantly with increasing GOLD severity of CPD ($p<0.05$ all). Severe COPD was associated with significantly low hemoglobin, higher total platelet count, higher PLR, higher MPV, higher PDW and higher plateletcrit in comparison to patients with mild COPD ($p<0.05$). This is consistent with the findings of a similar study conducted by Kalemci et al. (2018). They found an increase in PDW, MPV, PCT, PLR and RDW values with an increase in the severity of COPD. They also noted that patients in the severe COPD group had higher, PDW, MPV, PCT, and PLR values but had lower hemoglobin levels and lymphocyte count compared with the mild COPD group. On the other hand, among all platelet indices only PDW and MPV showed significant change with increasing clinical severity. This indicates a disjunction between platelet indices and clinical severity while a significant association between GOLD severity and platelet indices were noted.

An increase in PDW as the severity of COPD increased could be related to an elevation in the

thrombosis load and/ or increased inflammation that occurs as the disease becomes more severe. PDW was shown to increase in various pulmonary diseases other than COPD such as obstructive sleep apnea syndrome, pulmonary tuberculosis, pulmonary embolism and pulmonary hypertension.[17]

Increased MPV is a marker of platelet activation. The MPV acts as an acute phase reactant in inflammatory conditions depending on the severity of systemic inflammation. It has been shown to increase in low grade inflammations but to decrease due to intensive degradation of platelets in inflammatory regions in severe inflammatory conditions. In a study by Zhang et al the MPV was higher in patients with COPD compared with controls, and even higher in patients during acute exacerbations compared with those in the convalescence period. On the other hand, some other studies suggested that the MPV decreases in patients with inflammatory disorders including COPD[17] which is consistent with the findings of this study.

Low lymphocyte count is related with increased inflammation. Combined with the platelet count, the PLR reflects the inflammatory status in the body more accurately. Karadeniz et al found that the PLR was higher in patients with COPD during acute exacerbation compared with stable ones and healthy controls, and they concluded that the PLR might be a useful and easily accessible tool for evaluating the ongoing inflammation during the stable period and the disease severity during acute exacerbations in patients with COPD.[10] Results of this study were in line with those findings in terms of high PLR values in patients with more severe COPD.

1. No comparison was done among the findings in patients with different modalities of treatment prior hospitalization.

Patients with multiple diseases was not considered into the study.

Limitation

Conclusion

Platelet indices particularly MPV is associated with the severity of the COPD exacerbation. It is observed that the more severe the exacerbation the higher the value of MPV, Pct, PDW and PLR. Value of these indices also rise with the severity of airflow limitation in COPD (FEV_1).

References:

1. GOLD 2009. 'GOLD 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Inititiative For Chronic Obstructive Lung Disease, 1–139.
2. Lozano, R. Naghavi, M. Foreman, K. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systemic analysis of Global Burden of Disease Study 2010', Lancet. 2012;380(9859): 2095-128.
3. Mathers, CD & Loncar, D. Projections of global mortality and bren of disease from 2002 to 2030',PLos Med. 2006;3(11): e442.
4. Wedzicha, JA. & Seemngal, TA. COPD exacerbations: defining their cause and prevention', Lancet. 2007;370(9589) 786-96.
5. Mohan, A. Premananda, R. Reddy, L.N., Rao, M.H., Sharma, S.K.Kamity, R. & Bollineni, S. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission in intensive care unit, BMC Pulmonary Medicine. 2006;6(1): 7.
6. Cazzola, M. MacNee, W. Martinez, F.J. Rabe, K.F. Franciosi, L.G., Barnes, P. J. Brusasco, V. Burge, P.S. Calverley, P.M.A. Celli, B.R. & Jones, P.W. Outcomes of COPD pharmacological trial: from lung function to biomarkers',European Respiratory Journal. 2008;31(2):416-469.
7. Briggs, C, Mellors, I, Roderick, A, Ward, A, O'Malley, C, Barker, J, De La Salle, B, McTaggart, P, Hyde, K & MacHin, SJ. Quality counts: New parameters in blood cell counting, International Journal of Laboratory Hematology. 2009;31(3):277–297.
8. Mahdavi-Zafarghandi, R, Shakiba, B, Keramati, MR & Tavakkoli, M. Platelet volume indices in patients with varicocele, Clinical and Experimental Reproductive Medicine. 2014;41(2):92–95.

9. 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', Journal of Thoracic Disease. 2017;9(6): 1509–1516.

10. Bahadori, K & FitzGerald, JM. Risk factors of hospitalization and readmission of patients with COPD exacerbation - Systematic review, International Journal of COPD. 2007;2(3): 241–251.

11. Alam, DS, Chowdhury, MA, Siddiquee, AT, Ahmed, S & Clemens, JD. 'Prevalence and determinants of chronic obstructive pulmonary disease (COPD) in Bangladesh', COPD: Journal of Chronic Obstructive Pulmonary Disease. 2015;12(6): 658–667.

12. Hossain, AM & Islam, K. Prevalence and risk factors of Chronic Obstructive Pulmonary disesae (COPD) in Dhaka City Bangladesh', Chest. The American College of Chest Physicians. 2009;136(4): 90S-b–91S.

13. 13. Ntritsos, G, Franek, J, Belbasis, L, Christou, MA, Markozannes, G, Altman, P, Fogel, R, Sayre, T, Ntzani, EE & Evangelou, E. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis', International Journal of Chronic Obstructive Pulmonary Disease. 2018;13: 1507–1514.

14. Khandker, NN, Biswas, T, Khan, ANS, Hasib, E & Rawal, LB. Socio-demographic characteristics and tobacco use among the adults in urban slums of Dhaka, Bangladesh, Tobacco Induced Diseases. Tobacco Induced Diseases. 2017;15(1):1–8.

15. Grigsby, M, Siddharthan, T, Chowdhury, MAH, Siddiquee, A, Rubinstein, A, Sobrino, E, Miranda, JJ, Bernabe-Ortiz, A, Alam, D & Checkley, W. Socioeconomic status and COPD among low-and middle-income countries', International Journal of COPD. 2016;11(1):2497–2507.

16. Karadeniz, G, Aktoçu, S, Erer, OF, Kir, SB, Doruk, S, Demir, M & Sonat, K. Predictive value of platelet-to-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease, Biomarkers in Medicine. 2016;10(7):701–710.

17. Zhang, S, Cui, YL, Diao, MY, Chen, DC & Lin, ZF. Use of platelet indices for determining illness severity and predicting prognosis in critically ill patients. Chinese Medical Journal. 2015;128(15):2012–2018.