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THE ROLE OF MEAN PLATELET VOLUME IN THE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Studies have supported the correlation between mean platelet volume and COPD. However, there are limited data on the relationship between COPD exacerbation and mean platelet volume. **Aim:** This study was aimed to evaluate the mean platelet volume trend in patients with COPD exacerbation. **Materials and Methods:** This was a prospective study in which 80 patients with acute COPD exacerbation were enrolled at Tishreen University Hospital, Lattakia during the period between 2019 - 2020 . The levels of mean platelet volume, C-reactive protein, complete blood count, and percent of-predicted FEV_1 were measured in subjects at admission (exacerbation period) and after 3 months (stable period). **Results**: Subjects in the exacerbation period had significantly higher levels of C-reactive protein ($P<0.0001$), white blood cell count ($P<0.0001$) and percentage of neutrophils ($P<0.0001$) and lower percent-of-predicted FEV_1 than in the stable period ($P<0.0001$). Mean platelet volume levels were significantly decreased in the exacerbation period($P<0.0001$). Mean platelet volume levels correlated negative significantly with increase of C-reactive protein level in the exacerbation period ($r = - 0.342$, $p<0.001$) and in the stable period)$r = -0.168$, $p=0.0347$). **Conclusion:** Mean platelet volume may be an inflammatory marker in exacerbation of COPD.

KEYWORDS: mean platelet volume, exacerbation, COPD, inflammation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, according to the World Health Organization, it is the fourth cause of death in the world, and is expected to become the third cause of death by 2020.[1]

There is much evidence that the inflammatory response in COPD is not limited to the lungs. There are many systemic sequelae of the disease attributable to systemic inflammation. It has been established that stable COPD is associated with low-grade systemic inflammation as demonstrated by an increase in blood leukocytes, acute phase proteins such as C-reactive protein (CRP), fibrinogen, tumor necrosis factor alpha (TNF-a), endothelin-1, interleukin - 6 and circulatory leukocytes.[2] COPD exacerbation is described as an acute worsening of respiratory symptoms accompanied by a different degrees of physiological deterioration.[3] According to the World Health Organization (WHO), the US National Heart Diseases and Lungs Institute (US NHLBI), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), exacerbation is defined as: "An event in the natural course of the disease characterized by a change in the patient's baseline pulmonary symptoms (dyspnea, cough, and/or sputum) that is beyond normal day to day variations, is acute in onset, and may warrant a change in regular medications in a patient with underlying COPD".[4]

COPD exacerbations are associated with an increase not only in airway inflammation but also in systemic inflammation. Although the cause of this response is unclear, it is believed that it is due to spillover of the pulmonary inflammatory process. Systemic inflammation increases when acute exacerbation is associated with viral and bacterial infection, and serum levels of many inflammatory markers rise during the exacerbation, such as serum fibrinogen and CRP.[5] Mean platelet volume (MPV) is one of the platelet function indices. It reflects the platelet production rate and stimulation. MPV is a parameter generated by routine complete blood count test that is usually overlooked by clinicians.[6] Variations in MPV reflect changes in either

platelet stimulation level or platelet production rate.[7] MPV is known to increase when platelets are activated and their shape changes from disc to spherical, so MPV is an easy-to-measure laboratory marker for platelet activation.[8] Studies have shown that MPV increases in thrombotic diseases (with a low degree of systemic inflammation) such as cardiovascular diseases, peripheral vascular diseases, venous thrombosis and arterial embolism.[9] In contrast, a decrease in MPV is observed in inflammatory diseases (with a higher degree of systemic inflammation) such as rheumatoid arthritis and ulcerative colitis.[10,11]

Since both localized and systemic inflammation play an important role in both stable and acute exacerbation of chronic obstructive pulmonary disease, any change in platelet activity in response to this inflammation may cause a change in MPV.[12] MPV is a simple, inexpensive test that is performed as part of a routine complete blood count (CBC) obtained to assess patients with acute COPD exacerbation.

However, the association of mean platelet volume with COPD exacerbation has not yet been adequately evaluated. In recent years, there have been only limited studies evaluating this issue with controversial results. Some studies have shown that mean platelet volume levels are lower during exacerbation compared with the stable phase of COPD.[13,14] whereas a report found that this association is not statistically significant.[15]

The aim of the present study was to investigate the relationship between exacerbations and mean platelet volume trend in subjects with COPD and to clarify its significance as an inflammatory biomarker in COPD exacerbation.

MATERIALS AND METHODS

We studied 80 subjects aged 40 years and over who were hospitalized with a diagnosis of COPD exacerbation in the Department of Pulmonary Medicine in Tishreen University Hospital, Lattakia, Syria during the period between December 2019 - December 2020. All were receiving regular inhaled long-acting ß$_2$-agonists, regular inhaled glucocorticoids, and inhaled tiotropium bromide. Patients were evaluated on admission and were re-evaluated later in the stable phase. COPD exacerbation was diagnosed by the presence of sustained (lasting ≥ 48 h) increased breathlessness or dyspnea, increased cough or sputum production, or a sputum color change that was beyond normal day-to-day variations, was acute in onset, and led to an increase in the use of maintenance medications and/or supplementation with additional medications for patients with COPD, according to Global Initiative for Chronic Obstructive Lung Disease guidelines.[4] Stable state was defined as the absence of significant changes in symptoms beyond the expected daily variation, along with no requirements for increases in treatment at 3 months.

Also, COPD was diagnosed according to the above guidelines based on past smoking history, clinical evaluation, and pulmonary function tests showing irreversible air flow obstruction.[4]

We excluded from the study patients with coronary artery disease, acute heart failure, pneumonia, pulmonary thromboembolism, diabetes mellitus, history of cystic fibrosis, malignancy, connective tissue disease, or inflammatory bowel disease that could affect the mean platelet volume. Also, patients with blood disorders (anemia, thrombocytopenia), immune diseases, patients with prior treatment with anticoagulant regimens or anti-platelet medications were excluded.

The institutional review board of the hospital approved the research protocol, which complied with the 2000 Declaration of Helsinki, and all subjects consented to participate in the study.

1- Clinical examination

All the participants underwent a complete clinical examination.

2- Spirometric function test

Spirometry was performed to confirm the COPD diagnosis when patients were in the stable phase, also it was performed during hospitalization of exacerbation. Patients were instructed to perform forced expiration until three acceptable measurements were obtained according to the European Respiratory Society criteria.[16] Each recorded result was expressed as a percentage of the predicted value for that parameter. Predicted values were calculated according to the system developed by Quanjer et al.[17] These results were used to define disease severity according to the GOLD classification – namely.[18]

- Stage I (mild), FEV1/FVC<70% and FEV1≥80% predicted
- Stage II (moderate) FEV1/FVC<70% and 50%≤FEV1<80% predicted
- Stage III (severe), FEV1/FVC<70% and 30% ≤ FEV1 < 50% predicted
- Stage IV (very severe), FEV1/FVC<70% and FEV1<30% predicted or FEV1<50% predicted plus chronic respiratory failure.

Baseline spirometric function parameters were obtained during exacerbation and repeated during the follow-up visit after improvement (stable phase).

3- Biochemical measurements

Venous blood samples were collected from participants in the morning between 9.00 and 10.00 a.m. after an overnight fast of at least 10 h. Venous blood samples were collected into K3 EDTA (15%) Becton Dickinson Vacuum tubes (Shandong Weigao Group

Medical Company, China) and mixed gently. CBC was measured within 1–2 h of blood sampling using Nihon

Codon fully automatic hematological analyzer (Nihon Kohden, Tokyo, Japan). The hematological analyzer was calibrated using a standardized, commercially available calibrator kit. CBC [white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelet count, MPV] was measured. CRP level was determined by the nephelometric method (Clauss, Dade Behring, Marburg, Germany).

The expected MPV values in our laboratory ranged between 9.4 and 12.3 fl. CRP levels and CBC of patients with acute COPD exacerbation were recorded. CBC and CRP measurements were taken at first administration of medications for exacerbation and before initiation of any additional therapies and repeated 2 weeks later after improvement.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) (version 20) as well as Excel 2010. Predictive value less than 0.05 was considered statistically significant.

All data are presented as mean ± SD for continuous variables. The differences in measured parameters between the exacerbation and the stabilization COPD phases were determined using t- student test, ANOVA one – way test. The χ2-test was performed for all categorical variables.

The Pearson's correlation analysis was used to investigate the relationship between two quantitative variables (MPV and CRP).

RESULTS

Characteristics of patients are summarized in Table 1. The mean age of COPD patients in our study was 62.7 ± 8.5 years, 60 (75%) were men, and 69 (86.2%) were smokers. 14 (17.5%) patients had mild COPD, 28 (35%) patients had moderate COPD, 25 (31.3%) patients had severe COPD, and 13 (.16%) patients had very severe COPD. The comparison of measured parameters in exacerbation and stable COPD is shown in Table 2. Patients in the COPD stable phase had significantly higher levels of FEV_1 ($P < 0.0001$). Patients in the COPD exacerbation phase had significantly higher levels of C-reactive protein, WBC count, and neutrophil percentage than in the period of stable disease ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). There were no significant differences regarding the platelet count, or hemoglobin concentration between COPD exacerbation and stable COPD phases (P= 0.139, P=0.266, respectively). The mean platelet volume levels were significantly lower in the exacerbation period compared with stable COPD ($P < 0.001$).

We compared MPV values for COPD patients in the exacerbation phase as well in the stable phase after classifying patients according to the grade of COPD severity (Table 3). The comparison was made using the ANOVA one-way test and there was no statistically significant difference in the mean MPV values between the different degrees of COPD severity during the exacerbation phase neither in the stable phase ($P = 0.187$, P=0.857, respectively). The Pearson correlation coefficient of MPV with CRP after adjustment for age, gender, and smoking status is presented in Table 4. There was a significant negative correlation between MPV and CRP during the exacerbation phase ($r = -0.342$, $P <0.001$) (Fig. 1). Also, There was a significant negative correlation between MPV and CRP during the stable phase ($r = -0.168$, P= 0.0347) (Fig. 2).

DISCUSSION

This study was conducted with the aim of assessing the relationship between the mean platelet volume (MPV) and the COPD exacerbation. The study included 80 patients diagnosed with COPD exacerbation, who were subsequently followed in the recovery phase (stabilization phase) after 3 months. This observational descriptive before – after study reveals that the mean platelet volume levels in subjects with COPD exacerbation decreased compared with the stable period ($P<0.05$).

Table 1: Baseline Characteristics of the patients.

Characteristics		Number of patients	Percent (%)
Age (years)	40 – 49	15	18.8%
	50 – 59	28	35%
	60 – 69	30	37.5%
	70 – 73	7	8.7%
Gender	Males	60	75%
	Females	20	25%
Smoking	Non – smoker	11	13.8%
	Smoker (ex/current)	69	86.2%
COPD severity	Mild	14	17.5%
	Moderate	28	35%
	Severe	25	31.3%
	Very severe	13	16.3%

Table 2: Comparison of Measured Parameters of Subjects in Exacerbation Phase and Stabilization Phase of COPD.

	COPD Exacerbation phase	COPD Stable phase	t- test	P-value
FEV_1	39.3 ± 12	48.2 ± 15	4.14	<0.0001
FEV1/FVC	44.8 ± 13.3	50.1 ± 14	2.454	0.0152
CRP (mg/dl)	41.2 ± 22	6.7 ± 3.8	13.82	<0.0001
WBC	12.1±2.3	7.26± 2.14	13.7	<0.0001
Neutrophils	79 ± 8.8	70 ± 6	7.55	<0.0001
Platelet count	226 ± 71	241 ± 56	1.48	0.1398
MPV	8.6 ± 0.9	9.5 ± 0.9	6.32	<0.0001
Hemoglobin	14.8 ± 1.7	15.1 ± 1.7	1.11	0.266

Table 3: Correlation between MPV and grade of severity of COPD.

MPV (fl)	grade of severity				P-value
	Stage I (mild)	Stage II (moderate)	Stage III (severe)	Stage IV (very severe)	
MPV during Exacerbation	8.1 ± 1.1	8.8 ± 1.2	8.4 ± 0.9	8.3 ± 1.07	0.187
MPV during Stable phase	9.1 ± 1	9.8 ± 1.07	8.9 ± 1.1	9.4 ± 0.89	0.85

Table 4: correlation of MPV with CRP after adjustment for age, gender, BMI and smoking status.

	r	P- value
MPV and CRP exacerbation	-0.342	<0.001
MPV and CRP stable	-0.168	0.0347

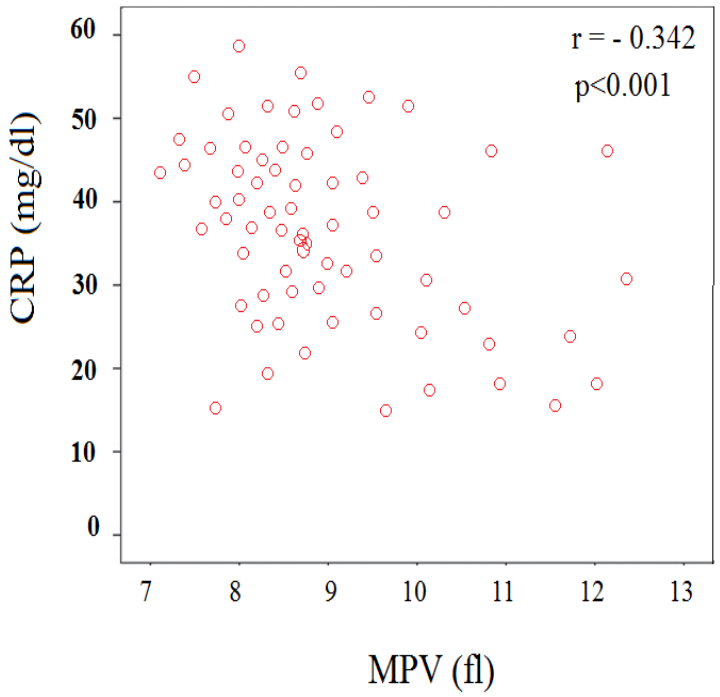

Figure 1: The relationship between MPV and CRP during the exacerbation phase.

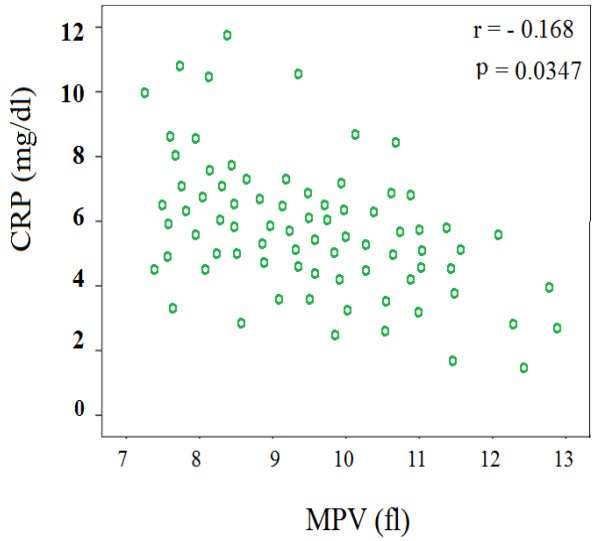

Figure 2: The relationship between MPV and CRP during the stable phase.

The mean platelet volume levels were negatively correlated with an increased C-reactive protein in patients with COPD exacerbation, as well as in patients with stable disease. Consequently, the results of our study suggest that MPV may be a helpful inflammatory biomarker indicating COPD exacerbation. With regard to the changes in mean platelet volume levels, our findings are in line with the results of a study of Ulsali et al,[13] in Turkey, 2012 which included 47 COPD patients with exacerbation who were reevaluated after 3 months (stabilization phase), they demonstrated that in the exacerbation period of COPD, mean platelet volume levels were decreased. On the contrary, they failed to detect a correlation between mean platelet volume and C-reactive protein, probably due to their small sample size, the baseline increased level of C-reactive protein, or the high mean platelet volume levels in the stable period. In the study of Agapakis et al,[19] in Greece, 2016 that included 81 COPD patients during the exacerbation period of COPD, who were reevaluated after 3 months (stabilization phase), they found that MPV levels during exacerbation were decreased compared to the stability phase. They also found that the mean platelet volume levels were correlated with an increased C-reactive protein and increases in both the relative proportion of neutrophils and the WBC count in subjects with COPD exacerbation, they concluded that MPV can be considered as a useful inflammatory marker indicating COPD exacerbation, especially at the MPV level> 8.2 fl, which distinguishes acute exacerbation from stable disease with 80% sensitivity and 76% specificity. In the study of Wang et al,[14] in China in 2013 that included 70 COPD patients during exacerbation and were reassessed in stability, the MPV levels during exacerbation were significantly lower compared to the stability status. Consistent with the results of our study, there was a significant negative correlation between MPV and CRP values during exacerbation as well as in the stabilization phase.

In the study of Eman Ali et al,[20] in Egypt, 2016 that included 40 COPD patients during exacerbation and they were reassessed in the case of stability, the MPV levels during exacerbation were significantly decreased compared to the stability phase. Contrary to our study and the previous studies, a study of Koçak et al[21] in Turkey, 2017 included 40 COPD patients with exacerbation and 40 patients with COPD in the stabilization phase, they showed an increase in MPV levels during exacerbation compared to the stable disease. In our study, there was no significant difference in the mean MPV values between the different degrees of COPD severity during exacerbation neither during the stabilization phase, consistent with Ulsali et al[13] and Wang et al.[14]

The literature does not support an accurate mechanism to fully explain these results, so we'll try to formulate some explanations. First of all, since the inflammation is a core feature of COPD exacerbation, it could be the cause of such a change in level of mean platelet volume. This present inflammatory response, caused mostly by bacterial infections of lower airways, is higher than in the stable disease.[22] Potential mechanisms for this increased systemic inflammation in COPD exacerbation include: (1) spillover of inflammatory mediators from the pulmonary compartment; (2) an inflammatory reaction to tissue hypoxia; and (3) a reaction induced by the pro-inflammatory bacterial product lipopolysaccharide.

Several studies showed that inflammatory markers, such as circulating neutrophil numbers, C-reactive protein, fibrinogen, interleukin-6, interleukin- 8, and soluble intercellular adhesion molecule 1, are increased during COPD exacerbation. The intensity of inflammation during COPD exacerbation could lead to reverse results (ie, increased mean platelet volume). Furthermore, increased levels of proinflammatory cytokines and C-reactive protein can lead to the production of more

reactive large platelets. which explains the results of the Koçak et al study.[21]

At the same time, COPD exacerbation has been associated with a prothrombotic state. Elevated levels of von Willebrand's factor, D-dimer, and prothrombin fragment 1_2, being surrogate markers for inflammation, endothelial damage, and clotting activation, respectively, have been measured during an exacerbation of COPD.[24]

A number of studies have demonstrated that subjects with COPD have an increased platelet count and also increased platelet activation in stable disease and further in the exacerbation period.[25,26] However, this platelet activation can follow different patterns as to mean platelet volume values in various diseases. In particular, in diseases with low-grade chronic inflammation that predisposes to thrombosis, such as cardiovascular disease or atherosclerosis (tendency to hypercoagulability), mean platelet volume levels are increased. In contrast, in diseases with high-grade inflammation, such as active rheumatoid arthritis, inflammatory bowel disease, and familial Mediterranean fever, mean platelet volume levels are reduced and normalized by anti-inflammatory therapy.[10,11] In our study, COPD exacerbation was associated with a significant decrease of mean platelet volume levels, such as in the high-grade inflammation diseases. However, because the great majority of severe COPD exacerbations requiring hospitalization are infectious in etiology, a key difference from the previous inflammatory findings is that in the exacerbation period, an infection is present. It could be argued that infections of airways may trigger abnormalities in inflammation and thrombosis markers, such as mean platelet volume, a link between inflammation and thrombosis. Along these lines, it has been found that children with cystic fibrosis have decreased levels of mean platelet volume during the exacerbation period compared with the stable phase.[27] Similarly, mean platelet volume levels in subjects with asthma with exacerbations were lower compared with those in subjects with stable asthma.[28]

Finally, the possibility cannot be excluded that the reduction in mean platelet volume is due to the consumption or sequestration of the large activated platelets in the vasculature.

CONCLUSION

The mean platelet volume levels in subjects with COPD exacerbation decreased compared with the stable period ($P<0.05$). The mean platelet volume levels were negatively correlated with an increased C-reactive protein in patients with COPD exacerbation, as well as in patients with stable disease. There is no significant difference in MPV between the different degrees of COPD severity during the exacerbation as well as in the stabilization stage.

RECOMMENDATIONS

MPV has shown that it can be a helpful inflammatory biomarker indicating the presence of acute COPD exacerbation, it is a simple test routinely performed with CBC analysis. Therefore, we recommend that it be approved as an additional marker alongside other clinical, laboratory and radiological parameters.

We recommend conducting further studies about the possibility of adopting MPV as a parameter to determine COPD patients at risk of acute exacerbation, as one of the disadvantages of this study is that it did not assess the number of exacerbations during the previous year.

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