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Chronic Obstructive Pulmonary Disease and Platelet Indices: An Indicator of Disease Severity

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Abstract

Background: Researchers recently found that megakaryocytes and hematopoietic progenitor cells can be found in the lungs. Therefore, during chronic obstructive pulmonary disease (COPD), lung damage may also affect platelet function and number.
Objectives: Our study investigated the association between platelet indices and disease severity in chronic obstructive pulmonary disease patients.
Methods: This cross-sectional study was conducted at Imam Reza (AS) and Ghaem (AS) hospitals in Mashhad in 2021. The study was conducted on patients with stable COPD at the lung clinics of these centers and non-COPD outpatients referred to the internal clinic. In both groups, the demographic and clinical information of the patients was recorded, followed by the patients' platelet indices. The platelet indices of COPD patients were compared with non-COPD patients in addition to an intergroup analysis based on disease severity defined by the global initiative for chronic obstructive lung disease (GOLD) classification.
Results: There were 100 patients in the study, among whom 50 (50%) had COPD. Neither of the groups differed significantly in age ($P = 0.85$) or gender ($P = 0.68$). Compared to the case group, the mean platelet volume (MPV) of non-COPD subjects was significantly higher ($P = 0.01$), but other platelet indices were not significantly different ($P > 0.05$). Comparing platelet indices between different stages of COPD demonstrated that the mean platelet volume was significantly different ($P = 0.04$), while others were not ($P > 0.05$).
Conclusions: According to this study, COPD patients have a lower MPV value than non-COPD individuals.

Keywords: COPD, Mean Platelet Volume, PLT, MPV, PDW, PLCR

1. Background

Chronic obstructive pulmonary disease (COPD) is a disease that causes irreversible airflow obstruction in the lungs. In 2015, over 174.5 million people were affected by this disease, and more than 5.4 million deaths are expected by 2060 due to COPD and its complications (1). Shortness of breath and cough are the primary symptoms of this condition (2). Several factors contribute to the development of COPD, including an imbalance between protease and antiprotease, chronic inflammation, and oxidative stress (3, 4). In addition to the pulmonary manifestations of COPD, it has been demonstrated that most COPD patients also experience systemic symptoms. Accordingly, some COPD endotypes and phenotypes have been postulated; however, additional phenotypes have yet to be identified (5). Spirometry assists in determining the degree of respiratory airflow obstruction. Moreover, using the forced expiratory volume in one second (FEV1), the global initiative for chronic obstructive lung disease (GOLD) grades COPD severity (6).

Recent research has demonstrated that platelets, in addition to controlling homeostasis and coagulation, play an important role in modifying inflammatory and immunomodulatory responses through the release of specific molecules (7, 8). Platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW) are the parameters that characterize these alterations. Platelets attract leukocytes to the site of inflammation, and these cells engage in several intracellular and intercellular processes that participate in subsequent atherogenic and

thrombotic events (5, 9). There is a scientific consensus that MPV and PDW are indicative of platelet activation and are frequently elevated in individuals who are at risk for thrombosis and atherosclerosis (9, 10). Mean platelet volume was also found to be decreased in COPD patients due to the inflammatory burden manifested in exacerbations, extensive platelet destruction, or the use of larger platelets at the inflammation site during the intercellular interactions (11, 12); however, these findings are not consistent. During platelet hyperproduction, the bone marrow releases immature and larger platelets, increasing PDW and reflecting the variety of platelet sizes (13). The precursors of platelets, megakaryocytes, can migrate from the bone marrow to the lungs, where interstitial tissue and capillaries trap them. Consequently, the lungs produce approximately half of the platelets (14). Moreover, a major cause of mortality in COPD patients with pulmonary heart disease is pulmonary artery thrombosis, which is also linked to platelet aggregation (15).

2. Objectives

In order to develop practical clinical guidelines, the present study was conducted to investigate the association between platelet indices and the severity of the disease in COPD patients.

3. Methods

3.1. Design of the Study

The cross-sectional analytical study was conducted in 2021 in two Mashhad referral hospitals, Imam Reza and Ghaem. The study involved 50 stable COPD patients and 50 non-COPD (control) individuals.

All participants signed informed consent forms.

In the study group, patients with COPD were screened for eligibility during ambulatory visits at the lung clinics of the hospitals mentioned above. Fifty patients, mostly current or former smokers aged $>$ 40 with a diagnosis of COPD according to GOLD guidelines, were included. All patients were diagnosed by a pulmonologist based on clinical data, current symptoms, and spirometry measurements. Chronic obstructive pulmonary disease was confirmed if FEV1/FVC $<$ 70, and the patients were divided into 4 categories based on FEV1: (GOLD 1: FEV1 $\geq$ 80, GOLD 2: 50 $\leq$ FEV1 $<$ 80, GOLD 3: 30 $\leq$ FEV1 $<$ 50, GOLD 4: FEV1 $<$ 30).

Also, COPD patients were sub-grouped into 4 categories based on COPD Assessment Test (CAT) and number of exacerbations during the last year (ABCD).

All COPD patients included in the study had to be in a stable phase of the disease (no exacerbation of symptoms or no change in relative medication during the last month).

The exclusion criteria for COPD patients were as follows: (I) unwillingness to participate; (II) the presence of systemic inflammatory diseases, severe liver disease, severe kidney failure, malignant diseases, bone marrow failure, active infection, diabetes with severe complications, right heart failure or pulmonary hypertension, lung diseases other than COPD, and iron deficiency anemia; (III) history of platelet-modifying drugs, including aspirin and Plavix.

The control group consisted of 50 non-smokers and non-COPD patients who were aged $>$ 40 and visited the internal medicine clinic for periodic examinations and checkup tests. Their health state was established based on anamnestic data. Control individuals met the same exclusion as the COPD patients. Additionally, they didn't have any history of baking bread, smoking, or any lung disease.

We took a careful and complete history and performed a thorough physical examination in both groups and excluded any patient with cancer and any clinical evidence of right heart failure or pulmonary hypertension according to history, physical examination, and ECG findings.

We excluded any individual with a known diagnosis of iron deficiency anemia and also those with hemoglobin (Hb) $<$ 13 g/dL in males and Hb $<$ 12 in females (according to WHO criteria for anemia).

In this project, the following parameters were assessed in the blood collected from the participants: Complete blood cell count (CBC), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine (Cr), and platelet indices [PLT, MPV, PDW, and platelet-large cell ratio (PLCR)]. Due to the invasive nature of arterial blood gas (ABG), the blood gases of the COPD group were evaluated using a venous blood gas (VBG) test instead of an ABG. Following the collection of the data, the information collected in the two groups was recorded in their respective checklists, and platelet indices were compared between the 2 groups. A HI-801 CHEST spirometer was used to determine the FEV1 of the case group in accordance with the GOLD criteria. The FEV1 of group 1 was greater than 80%, the FEV1 of group 2 was between 50 and 80%, the FEV1 of group 3 was between 30 and 50%, and the FEV1 of group 4 was less than 30%. Additionally, the ABCD assessment of COPD patients was performed using the CAT. The patients completed the Persian versions of this questionnaire. Sigari and Ghafori (16) have examined and confirmed the validity of the Persian version of the CAT questionnaire.

3.2. Statistical Analysis and Sample Size Estimation

In the current research, descriptive statistics such as mean, standard deviation, and frequency were used to describe the data. An independent *t*-test was used to compare normal quantitative variables between the two groups with and without COPD. Mann-Whitney tests were used to compare non-normal quantitative variables between the two groups. ANOVA and Kruskal-Wallis tests were also used to examine normal and non-normal quantitative variables in more than two groups. Further, chi-square and Fisher's test were used to determine whether the frequency of qualitative variables differed between the 2 groups. This study utilized Stata software (Corp, College Station, Texas) version 12, and a significance level of less than 0.05 was considered significant.

In order to estimate the sample size, we used the study of Hlapcic et al. (5). Based on the formula for calculating the average in two populations in the statistical software PASS, a minimum of 50 subjects were obtained per group based on the mean and standard deviation of platelet index levels in two groups of COPD (263 ± 114.4) and non-COPD (196 ± 78) patients and an alpha error of 5% and statistical power of 90% were considered.

4. Results

There were 100 participants in the study, among whom 50 (50%) were in the COPD group and 50 (50%) were in the non-COPD group. There was an average age of 62.27 ± 8.70 years for the COPD group and 58.64 ± 11.76 years for the non-COPD group. According to the independent *t*-test results, there was no significant difference in age between the two groups (P = 0.85). Using Fisher's exact test, no significant differences were found between the genders in the two groups (P = 0.68). Also, the mean white blood cell (WBC) in the total study population was 7.47 ± 2.01 10^9/L, and the mean MPV was 9.42 ± 1.24 fL, respectively. Furthermore, the mean number of exacerbations was 0.82 ± 0.82 in total. Table 1 provides a summary of the detailed baseline laboratory results of the entire study population.

Additionally, we evaluated the patients according to the GOLD and ABCD criteria and their CAT scores. One patient (2%) was classified as GOLD 1, 33 (66%) as GOLD 2, 14 (28%) as GOLD 3, and two (4%) as GOLD 4. In addition, 2 (2%) of the patients were categorized as A, 37 (74%) as B, 0 (0%), and 11 (22%) as D. In terms of CAT scores, two patients (4%) were below ten, and 48 (96%) were equal to or higher than ten. Table 1 compares the platelet indices of COPD patients with those in the non-COPD group. The MPV of the non-COPD group was significantly higher than that of the COPD group (P = 0.01), as can be seen in Table 1.

As for the association between platelet indices and COPD severity, Table 2 shows the correlation between platelet indices and the severity of COPD based on the GOLD criteria. As can be seen, there was a significant difference between the MPV values in the two groups (P = 0.048).

The correlation between platelet indices and ABCD classification is presented in Table 3. Among all the investigated platelet indices, there were no significant differences between the different groups of patients (P > 0.05).

Table 4 shows the correlation between laboratory findings and CAT scores of COPD patients with their platelet indices. The results of the study demonstrated that hemoglobin levels were significantly correlated with platelet counts (P = 0.02), and the WBC count was significantly correlated with platelet counts (P = 0.018).

5. Discussion

Platelet indices are a set of markers that provide insight into the function of the blood coagulation system. The PLT provides a useful indication of the formation and decay of platelets. Platelet distribution width indicates the variability in the size of platelets, while MPV indicates the generation of megakaryocytes and platelets. It has been shown that PDW and MPV are both markers of thrombopoiesis (15, 17). Our study showed there was no significant difference between the two groups in terms of platelet indices (including PLT count, PDW, and PLCR). Still, COPD patients had significantly lower MPV than the non-COPD group. Moreover, examining the correlation between platelet indices and laboratory findings revealed that hemoglobin levels were significantly and inversely related to PLT. Conversely, there was a significant and direct correlation between WBC count and the PLT; thus, patients with higher WBC had a higher PLT.

Several studies have demonstrated the importance of systemic inflammation in the pathophysiology of COPD, the correlation between inflammation during an exacerbation, and the severity of the disease (18-20). Regarding patient classification, most of our patients belonged to group B, although other research produced differing results. A large study in Turkey identified group A as their primary population, while another study reported group D as their primary population. Among the analyzed platelet indices, there was a significant difference between the two groups in only MPV, which was lower in the COPD group; previous studies partly support our results. Hlapcic et al. (5) analyzed the platelet indices in patients with COPD, and they reported that PLT, MPV, and PDW were lower in the COPD group. Furthermore,

Table 1. The Demographic and Laboratory Findings Among the Study Population [a]

Characteristic	Study Groups		P-Value
	COPD Group	Non-COPD Group	
Age	62.27 ± 8.70	58.64 ± 11.76	0.085
Gender (femal/male)	20/30	23/27	0.545
PCO_2 (mmHg)	45.77 ± 5.51	-	-
SPO_2 (%)	92.55 ± 1.84	-	-
CRP (mg/L)	8.23 ± 8.87	-	-
Hb (g/dL)	14.06 ± 1.79	-	-
WBC (10^9/L)	7.47 ± 2.01	-	-
Number of exacerbations	0.82 ± 0.82	-	-
Platelet count ($10^3/\mu L$)	237 (191.5 - 277)	236 (191.5 - 298)	0.98 *
MPV (fL)	9.15 (8.02 - 9.87)	9.7 (9.20 - 10.30)	0.01 *
PDW (fL)	13.35 ± 2.23	13.71 ± 7.74	0.75 **
PLCR (%)	23.87 ± 7.01	25.78 ± 8.45	0.47 **

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; MPV, mean platelet volume; PDW, platelet distribution width; PLCR, platelet-large cell ratio.
[a] Values are expressed as mean ± SD or median (IQR) unless otherwise indicated.

Table 2. The Association Between Platelet Indices and the Global Initiative for Chronic Obstructive Lung Disease Classification of Study Participants [a, b]

Characteristic	GOLD 1 (n = 1)	GOLD 2 (n = 33)	GOLD 3 (n= 14)	GOLD 4 (n = 2)	P-Value
Platelet count ($10^3/\mu L$)	162	241 (196 - 295)	225 (177 - 262)	288 (283 - 293)	0.19 *
MPV (fL)	12.7	9.1 (9.7 - 8.1)	9.6 (8.07 - 10.92)	7.15 (6.7 - 7.6)	0.04 *
PDW (fL)	17.10	13.01 ± 2.29	13.68 ± 1.93	14.30 ± 2.40	0.24 **
PLCR (%)	-	23.21 ± 9.07	24.06 ± 4.29	28	0.83 **

Abbreviations: GOLD, the global initiative for chronic obstructive lung disease; MPV, mean platelet volume; PDW, platelet distribution width; PLCR, platelet-large cell ratio.
[a] Values are expressed as mean ± SD or median (IQR) unless otherwise indicated.
[b] * Kruskal-Wallis test was used for comparison. ** One-way ANOVA was used for comparison.

Table 3. The Association Between Platelet Indices and ABCD Classification of Study Participants [a, b]

Characteristic	A (n = 2)	B (n = 37)	D (n = 11)	P-Value
Platelet count ($10^3/\mu L$)	277 (228 - 326)	247 (196 - 280)	220 (183 - 268)	0.44 *
MPV (fL)	7.4 (12.7 - 2.9)	9.1 (8.1 - 9.7)	9.7 (8 - 11)	0.20 *
PDW (fL)	14.55 ± 1.34	13.30 ± 2.29	13.29 ± 2.22	0.74 **
PLCR (%)	36 ± 6.12	22.87 ± 7.02	23.24 ± 5.84	0.21 **

Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width; PLCR, platelet-large cell ratio.
[a] Values are expressed as median (IQR) or mean ± SD.
[b] * Kruskal-Wallis test was used for comparison. ** One-way ANOVA was used for comparison.

in another study conducted by Wang et al. (12) it was shown that MPV was lower in the COPD group. Several studies have shown that as hypoxemia worsens, MPV and thrombocyte aggregation increase, suggesting that the absence of oxygen may affect platelet activity, volume, and aggregation (21). Furthermore, research has been conducted to determine whether MPV can be used to predict COPD exacerbations and pulmonary hypertension (22, 23). A study by Koç et al. (11) found that, although there was a significant difference between the two groups in terms of MPV, there was no significant difference regarding PLT. Moreover, a recent systematic review indicated that COPD patients had significantly higher PLT than healthy individuals. Still, their MPV and PDW levels did not differ

Table 4. The Correlation Between Laboratory Findings and Chronic Obstructive Pulmonary Disease Assessment Test Scores of the Chronic Obstructive Pulmonary Disease Group with Platelet Indices [a]

Laboratory Index	Platelet Count	MPV	PDW	PLCR
SPO_2				
P-value	0.87 *	0.90 *	0.71 **	0.27 **
r	-0.022	0.018	-0.054	0.302
PCO_2				
P-value	0.55 *	0.36 *	0.49 **	0.61 **
r	0.087	0.133	0.100	0.141
Hb				
P-value	0.02 *	0.06 *	0.59 **	0.85 **
r	-0.332	0.264	-0.079	0.053
WBC				
P-value	0.01 *	0.42 *	0.23 **	0.41 **
r	0.337	-0.118	0.176	-0.226
CRP				
P-value	0.13 *	0.03 *	0.56 *	-
r	0.440	-0.592	-0.186	-
CAT				
P-value	0.15 *	0.37 *	0.37 *	0.30 *
r	0.207	-0.131	0.130	-0.284
Number of exacerbations				
P-value	0.97 *	0.39 *	0.21 *	0.93 *
r	0.004	0.125	0.184	0.023
FEV1				
P-value	0.96 *	0.59 *	0.65 **	0.90 **
r	0.007	0.078	-0.067	0.034

Abbreviations: Hb, hemoglobin; WBC, white blood cell; CRP, C-reactive protein; CAT, COPD Assessment Test; FEV1, forced expiratory volume in one second; MPV, mean platelet volume; PDW, platelet distribution width; PLCR, platelet-large cell ratio.
[a] * The Spearman correlation test was used for comparison. ** The Pearson correlation test was used for comparison.

significantly (24), showing the inconsistency between the literature. Nevertheless, MPV readings could be affected by a variety of factors, including age, gender, race, ethnicity, lifestyle, genetic background, venipuncture procedure, anticoagulant used, type of sample, as well as the nature of the study itself (25). Also, the variability in individual responses to disease changes should be considered a factor affecting MPV (10, 26).

On the other hand, different authors have also provided different reasons for their conflicting reports on the status of platelet indices. An increase in platelet count has been attributed to an underlying inflammatory state in COPD patients, which stimulates the bone marrow to produce platelets (5). In addition, some studies have stated that the reduction of MPV may be a result of the consumption of large platelets in inflammation sites, which leads to the presence of small platelets in the bloodstream (9, 25).

A minor finding of our study was that only MPV among the platelet indices was significantly associated with the disease severity. The MPV significantly decreased with increasing severity of COPD in the GOLD classification, but no such difference was observed in the CAT classification. In the majority of previous studies, the GOLD classification has been used. Based on the GOLD analysis, Pilaczynska-Cemel et al. (27) confirmed our findings and reported that PLT was not indicative of COPD severity. Despite this, Nunez et al. (28) and Huang et al. (29) observed that increased PLT was associated with more severe pulmonary dysfunction.

In this research, we did not measure ferritin levels for all participants. We excluded individuals with a known diagnosis of iron deficiency anemia and also those with Hb < 13 g/dL in males and Hb < 12 in females (according to WHO criteria for anemia).

However, considering evidence suggesting a possible relationship between PLT count and ferritin levels as well as Hb levels (30), not measuring ferritin levels could be a limitation of our study. It should be noted that previous studies did not recognize iron deficiency as an exclusion criterion (5, 31).

Additionally, we faced difficulties in recruiting a large number of patients for our study, and the sample size was inadequate. Since only outpatients were included in the study, the distribution of patients was not homogeneous according to GOLD staging, and the majority of patients belonged to group D.

Footnotes

Authors' Contribution: Study concept and design: S. N.; acquisition of data: M. A., S. N., M. M., F. E., and A. R.; analysis and interpretation of data: H. M. M., and A. R.; drafting of the manuscript: S. N.

Conflict of Interests: The authors declare no conflicts of interest.

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Informed Consent: The participants were properly informed about the study and provided informed consent.

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