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PLATELET ACTIVATION IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Several studies in COPD have shown an increase in platelet activity during acute exacerbation. However, platelet activity in stable COPD has been analyzed only in few studies. This study was undertaken to analyze the role of platelet activity in stable COPD patients. **Materials and methods:** We conducted a case-control study in a tertiary care, university-affiliated hospital. COPD patients and controls were matched for sex and age in a 1:1 matching ratio. We included only those patients who had quit smoking. Platelet parameters and pulmonary function tests were performed in both the groups. **Results:** Among the platelet indices, platelet to lymphocyte ratio (p-0.005) and mean platelet volume (p<0.001) were significantly higher in COPD cohort. Platelet distribution width showed statistically significant association with severity of COPD (p-0.003). Severity of COPD was negatively correlated with platelet to lymphocyte ratio (p - 0.002, r = -0.442) and platelet count (p - 0.039, r = -.299). Platelet to lymphocyte ratio was found to have positive correlation with platelet count (p < 0.001, r = 0.727). **Conclusion:** Our results suggest the presence of ongoing inflammation in stable COPD patients and hence, newer drugs which decrease the level of inflammatory markers may revolutionize COPD treatment. In addition, platelet indices may be useful for evaluating disease severity during stable phase.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease of the respiratory system and has extremely high morbidity and mortality rates. At present, COPD is the fourth highest cause of death worldwide and is expected to become the third leading cause of mortality by the year 2020.[1] Exacerbations of respiratory symptoms in COPD are of major importance because of their profound adverse effects like accelerated deterioration of lung function, poor quality of life, and increased mortality.[2] The pathogenesis of COPD involves systemic inflammation with abnormal inflammatory responses in the lungs.[3] The current treatment modalities cannot completely reverse COPD and hence treatment goal is symptom relief and prevention of disease progression. There is a lot of active research going into the role of inflammation in COPD and its treatment with anti-inflammatory agents.

Platelets play an important role in inflammatory processes. Platelet indices like Mean platelet volume (MPV) and platelet distribution width (PDW) correlates well with inflammation and have been investigated in different diseases like cardiovascular disease, rheumatoid arthritis, peripheral artery disease and inflammatory bowel disease.[4–8] In recent years, the platelet-to-lymphocyte ratio (PLR) has emerged as a potential inflammatory biomarker and has been evaluated in many conditions.[9,10] The aim of the study was to assess platelet parameters in stable COPD patients and to analyze its association with the severity of the disease.

MATERIALS AND METHODS

We conducted a prospective case-control study in Government medical college, Thiruvananthapuram during the period April 2012 to April 2013. COPD patients and controls were matched for sex and age in a 1:1 matching ratio. COPD was confirmed in patients with a FEV1/FVC ratio of less than 0.7, measured 20 minutes after the administration of salbutamol and COPD severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. COPD patients visiting the outpatient clinic were sequentially enrolled. The control group consisted of volunteers recruited from the same hospital who visited other outpatient clinics who did not have any comorbidity and had normal spirometry. COPD patients with an episode of exacerbation in the last 4 weeks were excluded. The stable disease group was not on oral steroid therapy (in the last 4 weeks) or long-term oxygen therapy. We also excluded patients and controls diagnosed with asthma in the past 5 years, current or former smokers with an abstinence time of less than 6 months, suspected diagnosis of infectious disease, surgery, or trauma in the last 30 days, diabetes, heart failure, chronic renal failure, pregnancy, stroke, malignancy and ischemic heart disease. The college ethics committee approved the research and all subjects

gave written informed consent to participate in the study. The participants were interviewed and data were collected through a standardized questionnaire. Spirometry was performed using a computerized spirometer in both cases and controls and blood sample was collected from all the participants and complete blood count parameters, including platelet counts, MPV, and PDW values were measured using a high sensitivity assay. The PLR was calculated from the ratio of platelets to lymphocytes. For measuring MPV, blood samples were obtained by venipuncture. The blood was collected in EDTA tubes. We analyzed the blood samples of all of the groups using an automatic blood counter after two hours of venipuncture. This period of time was waited to allow for the stabilization of platelet shape changes (Sysmex SE 9500, Roche). For measuring fibrinogen, blood samples were obtained by venepuncture. The blood was collected into Vacutainer tubes containing sodium citrate. The blood was immediately separated in to plasma and stored at -800 C. Fibrinogen was estimated using Clauss method using STA- Fib 2 kit in STA-Compact. Statistical analyses were performed using IBM SPSS version 20 for Windows. Independent samples *t*-test was performed for continuous variables and was expressed using the mean ± standard deviation and the median. Chi square test was performed for categorical data. Statistical significance was defined as p value <0.05.Univariate analysis was done to determine relative risk of mortality and comparison of means among more than two groups were analyzed by one-way ANOVA. Associations between the parameters were assessed using Spearman's correlation test for normally distributed data and Pearson's test for abnormally distributed data.

RESULTS

Forty eight COPD patients were included in our study in addition to 48 healthy individuals as control group. Baseline characteristics of the study participants are shown in table 1. All the individuals in our study were males. The complete blood count parameters of study participants are shown in table 2. The blood count parameters showed significantly higher leucocyte, neutrophil, and lymphocyte count in COPD patients. Among the platelet indices, PLR (p-0.005) and MPV (p<0.001) were significantly higher in COPD cohort. Platelet count and PDW did not show any statistically significant association with COPD cohort. However, PDW had statistically significant association with severity of COPD (p-0.003). Rest of the platelet indices did not show any association with the severity of COPD (Table -3). None of the platelet indices had statistically significant association with the number of prior exacerbations (Table - 4). Stable COPD patients were assessed in terms of correlation between platelet indices, leucocyte count and FEV1/ FVC ratio. The FEV1/FVC ratio was negatively correlated with PLR (p - 0.002, r = -0.442) and platelet count (p - 0.039, r = -.299). PLR was found to have positive correlation with platelet count (p < 0.001, r = 0.727) (Table–5).

Table 1: Baseline characteristics of the study participants.

	Case	Control
Age in years	62.6 ± 9.8	61.8 ± 8.9
Gender		
Male	48	48
Female	0	0
Occupation		
Manual labour	36 (75%)	28 (58.3%)
Semi-skilled labour	3 (6.3%)	9 (18.8%)
Skilled labour	9 (18.8%)	11 (22.9%)
Smoking status		
Ex-smokers	48 (100%)	0
Non-smokers	0	48 (100%)
Number of exacerbations in previous year		
1	18 (37.5%)	0
2	17 (35.4%)	0
3	13 (27.1%)	0
Elevated jugular venous pressure (mm Hg)	0	0
Systolic blood pressure (mm Hg)	135.7 ± 21.7	132.0 ± 14.5
Diastolic blood pressure (mm Hg)	82.3 ± 9.8	82.8 ± 9.4
Body mass index	21.82 ± 1.95	23.73 ± 2.09
Mean FEV1 (%)	60.33 ± 19.51	83.02 ± 5.30
Mean FEV1/FVC	0.61±.06	.81 ±.04

Table 2: Complete blood count parameters of the chronic obstructive pulmonary disease patients and controls.

Complete blood count parameters	Case	Control	p value
Mean hemoglobin (gm/dl)	13.2 ± 2	13.4 ± 1.0	0.384
Mean ESR (mm/hr)	20.71 ± 10.77	13.5 ± 8.03	0.001
Mean leucocyte count (/µl)	9664.2 ± 2656.1	8037.5 ± 1764.0	0.001
Mean neutrophil count (/µl)	6,861.8 ± 312.4	5047.28 ± 158.7	0.001
Mean platelet count (lakhs/µl)	2.23 ± 0.64	2.13 ± 0.38	0.372
Mean platelet volume (femtolitre)	9.1 ± 0.75	8.47 ± 0.45	<0.001
Platelet distribution width (%)	15.03 ± 1.81	15.15 ± 1.08	0.696
Platelet lymphocyte ratio	139.1 ± 174.5	86.9 ± 49	0.005

Table 3: Correlation between hematological parameters and severity of disease in stable COPD patients..

	GOLD class	N	Mean	Std. Deviation	Minimum	Maximum	F	p value
Leucocyte count (/µl)	1	13	10112.31	2656.87	6900.00	15000.00	1.605	.202
	2	24	9971.67	2965.04	5100.00	16000.00		
	3	9	8955.56	1191.75	6900.00	11000.00		
	4	2	6250.00	777.82	5700.00	6800.00		
Lymphocyte count (/µl)	1	13	2586.69	847.74	1346.00	4674.00	.126	.944
	2	24	2350.08	1314.84	472.00	5880.00		
	3	9	2332.22	1406.84	510.00	4510.00		
	4	2	2467.00	219.20	2312.00	2622.00		
Neutrophil count (/µl)	1	13	7323.37	2755.73	4235.00	12300.00	1.502	.227
	2	24	7422.15	2919.46	3060.00	13892.00		
	3	9	6444.22	1164.25	3920.00	7820.00		
	4	2	3658.00	981.46	2964.00	4352.00		
Platelet count (/µl)	1	13	214076.92	33589.34	160000.00	281000.00	.749	.529
	2	24	215541.67	78044.57	160000.00	530000.00		
	3	9	248333.33	61339.22	140000.00	330000.00		
	4	2	248000.00	11313.71	240000.00	256000.00		
PLR	1	13	91.73	36.51	54.36	174.59	.573	.636
	2	24	151.16	219.07	32.31	1122.88		
	3	9	184.19	179.88	47.62	561.59		
	4	2	101.13	13.57	91.53	110.73		
MPV (femtolitre)	1	13	9.06	0.64	7.50	10.30	.906	.446
	2	24	9.24	0.93	7.80	11.90		
	3	9	9.18	0.25	8.80	9.60		
	4	2	8.35	0.49	8.00	8.70		
PDW (%)	1	13	15.61	0.22	15.20	15.90	5.467	.003
	2	24	15.38	1.47	10.60	17.20		
	3	9	13.11	2.79	10.60	16.70		
	4	2	15.90	0.71	15.40	16.40		

Table 4: Correlation between hematological parameters and number of exacerbations in previous year in stable COPD patients.

	Number of exacerbations in previous year	N	Mean	Std. Deviation	Minimum	Maximum	F	p value
Leucocyte count (/µl)	1	18	9486.67	2683.92	5100.00	15000.00	1.007	.373
	2	17	10352.94	2480.70	7000.00	16000.00		
	3	13	9009.23	2835.21	5700.00	15100.00		
Lymphocyte count (/µl)	1	18	2511.33	992.99	670.00	4674.00	1.291	.285
	2	17	2646.35	1377.16	472.00	5880.00		
	3	13	1981.62	1087.57	510.00	4510.00		
Neutrophil count (/µl)	1	18	6785.60	2686.64	3060.00	12300.00	.363	.698
	2	17	7499.53	2402.83	3640.00	12800.00		
	3	13	6847.43	3017.57	2964.00	13892.00		
Platelet count	1	18	201277.78	34882.67	160000.00	281000.00	1.659	.202

(/µl)	2	17	233705.88	88024.69	140000.00	530000.00		
	3	13	237769.23	54251.20	169000.00	330000.00		
PLR	1	18	95.17	49.33	53.86	238.81	.993	.379
	2	17	154.55	253.61	32.31	1122.88		
	3	13	179.99	158.55	68.74	561.59		
MPV (femtolitre)	1	18	8.96	0.76	7.50	10.90	.826	.444
	2	17	9.23	0.60	8.30	10.60		
	3	13	9.28	0.93	8.00	11.90		
PDW (%)	1	18	15.49	0.49	14.20	16.10	1.023	.368
	2	17	14.89	2.06	10.60	16.70		
	3	13	14.59	2.52	10.60	17.20		

Table 5: Correlation between platelet indices and white blood cell, and severity of disease in stable COPD patients..

		MPV	PDW	FEV1/ FVC	TLC	Platelet count	PLR
MPV	Pearson Correlation		.051	-.074	-.057	-.075	.057
	Sig. (2-tailed)		.731	.618	.700	.612	.702
PDW	Pearson Correlation	.051		-.096	.080	-.136	.118
	Sig. (2-tailed)	.731		.515	.590	.356	.426
FEV1/FVC	Pearson Correlation	-.074	-.096		-.041	-.299*	-.442**
	Sig. (2-tailed)	.618	.515		.781	.039	.002
Leucocyte count	Pearson Correlation	-.057	.080	-.041		.222	.069
	Sig. (2-tailed)	.700	.590	.781		.129	.642
Platelet count	Pearson Correlation	-.075	-.136	-.299*	.222		.727**
	Sig. (2-tailed)	.612	.356	.039	.129		.000
PLR	Pearson Correlation	.057	.118	-.442**	.069	.727**	
	Sig. (2-tailed)	.702	.426	.002	.642	.000	

DISCUSSION

The results of the present study demonstrated that PDW and MPV were higher in the stable COPD patients compared with the controls. We did not detect a significant difference in platelet count and PDW among the subjects. We found a negative correlation between the FEV1/FVC ratio and PLR. We also found a negative correlation between the FEV1/FVC ratio and platelet count and a positive correlation between the platelet count and PLR; however, we did not find any correlation between the FEV1/FVC ratio and other platelet indices (MPV and PDW). Several studies, which examined platelet parameters in COPD patients have shown that increase in platelet activity occurred during acute exacerbation. Platelet activity in stable COPD has been analyzed only in few studies. This study was undertaken to analyze the role of platelet activity in stable COPD patients.

COPD is considered a systemic inflammatory disease. The levels of proinflammatory cytokines are increased, especially during exacerbation of the disease and these cytokines may cause activation of platelets by enhancing oxidative stress.[3,11] Low-grade inflammation has been demonstrated in stable COPD patients by elevation of white blood cell counts and levels of acute phase proteins. These inflammatory changes are associated with the increased comorbidities in these patients.[3,12] Several previous studies have reported on the potential use of markers of platelet activation as inflammatory markers; however, these studies have produced conflicting results.[13,14]

MPV is a marker routinely estimated by a full blood count analyzer and it correlates well with platelet activation. In our study, mean MPV of cases was 9.1 ± .75 and that of controls was 8.47 ± .4 and this difference was statistically significant ($p<0.001$). This finding agrees with many prior studies which reported elevated in COPD patients.[14–17] It was also demonstrated that MPV was higher in stable COPD and reduced during acute exacerbation.[15] Conversely, Biljak et al found reduced MPV in COPD, compared with controls.[13] The problem with this study is that, it was not age matched and had different smoking status. Present study was age matched and had similar smoking status. The possible hypothesis of higher platelet volume is bone marrow stimulation by hypoxia in COPD which results in secretion of larger platelets. The other hypothesis is increased sequestration of smaller platelets with larger platelets in the circulation. The consequences of larger platelets are increased platelet aggregation and release of active mediators which causes endothelial cell injury and results in a prothrombotic state. MPV did not differ significantly with COPD severity (p-0.446). This may be, at least in part, due to the small number of patients in some subgroups. Our study finding is in agreement with the previous works which also that MPV was not statistically associated with COPD severity.[13,15]

The PDW is another marker of platelet activation that indicates variability in platelet size. In the study PDW was lesser in COPD cohort but the difference was not statistically different (p-0.696). Similar to our findings, few studies have shown that the MPV decreased in COPD during acute exacerbation and they too did not found any difference in the PDW.[18,19] In contrast to our findings, a retrospective study reported that the PDW was elevated in COPD patients during the stable and exacerbation phases.[20] The significance of this finding in COPD is not known due to limited available data.

Only few studies have evaluated PLR in COPD patients. These studies reported that PLR was elevated both in the acute exacerbation patients and also in the stable COPD patients.[20,21] A retrospective study of COPD patients also showed a significantly negatively correlation of PLR with severity of airway obstruction. These findings were also confirmed in our study. PLR was significantly elevated in COPD patients (p-0.005) and PLR had a negative correlation with FEV1/FVC ratio (p - 0.002, r = -0.442). These findings support the hypothesis that COPD has an ongoing inflammatory process, even in patients with stable disease.

Platelet count was not significantly different between COPD cohort and control subjects. This finding was also noted in another prospective study which did not show a difference in platelet count between COPD and control group.[22] The platelet count was negatively correlated with FEV1/FVC ratio (p - 0.039, r = -.299) and had a positive correlation with PLR ($p < 0.001$, r = 0.727) (Table–5).

Our results highlight that stable COPD patients have a higher MPV and higher PLR than controls; indicating the presence of an ongoing inflammation even during the stable phase in COPD patients. Hence, newer drugs which decrease the level of fibrinogen and other inflammatory markers, like losmapimod may revolutionize COPD treatment. Moreover platelet count and PLR have negative correlation with severity of disease. These indices will be very useful for evaluating disease severity during stable phase markers which can be easily accessed by performing a complete blood count in a blood count analyzer. This study had few limitations. We acknowledge that the study had only male population and selection of biomarkers was incomplete. Sample size was relatively small and follow-up evaluation of these patients was not done.

CONCLUSION

In conclusion, the results of our study have demonstrated that stable COPD patients have a higher MPV and higher PLR than controls; in addition platelet count and PLR have negative correlation with severity of disease. Our results suggest the presence of ongoing inflammation in stable COPD patients and hence, newer drugs which decrease the level of inflammatory markers may revolutionize COPD treatment. In addition, platelet indices may be useful for evaluating disease severity during stable phase.

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