

Correlation of Platelet Indices with Clinical Profile in Elderly Patients: A Study in Rural Teaching Hospital

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Abstract

Introduction: There are evidence of age-related changes in platelet count and function, driven by changes in hematopoietic tissue, the composition of the blood and vascular health. Platelet count remains relatively stable during middle age but falls in elderly people. In this study we had tried to correlate platelet indices with the clinical profile like blood sugar, Lipid profile, blood pressure, Ischemic Heart disease and Chronic Obstructive Pulmonary Disease in elderly patients admitted in rural teaching hospital. **Materials and methods:** In this study, we have included 1000 patients among them 601 (60.1%) were males and 399 (39.9%) were females with the mean age of 66.02 ± 5.76 years. We studied platelet indices like plateletcrit (PCT), platelet distribution width (PDW) and mean platelet volume (MPV). **Observation and results:** The platelet indices (PCT, MPV and PDW) showed negative correlation with FBS and it was statistically significant ($p < 0.05$). The platelet indices showed positive correlation with blood pressure, negative with total cholesterol, positive with HDL, negative with LDL, negative with VLDL and negative correlation with TG. The platelet indices had negative correlation with IHD and COPD and they were statistically significant ($p < 0.05$). **Conclusion:** The platelet indices showed significant correlation with various clinical profiles of the elderly patients and they should be used routinely to aid in diagnosis.

Keywords: Platelet distribution width; Mean platelet volume; Platelet crit; Clinical profile; Elderly

Introduction

Aging is associated with an increased risk of functional dependence, hospitalization, and mortality. In India, the total population of elderly was 8.2% in the year 2011, which is expected to increase over the next four decades to 19% by 2050. In January 1999, Government of India adopted 'National Policy on Older Persons' which defined 'senior citizen' or 'elderly' as a person who is of age 60 years or above.^[1] The age-related physiological decline is intimately associated with poor quality of life, the need for long-term care and higher healthcare costs.^[2] Therefore, many recent studies have investigated the usefulness of various parameters as biomarkers for adverse clinical outcomes in the elderly.^[3-6] An important focus of this field is to determine whether typical parameters of automated blood cell counters demonstrate an association with adverse outcomes in the elderly. For example, total leucocytes and some subpopulations of leucocytes have been associated with frailty.^[7,8] In addition, red blood cell distribution width seems to be a good indicator of morbidity/mortality in older adults.^[9] Platelet indices have received an increasing amount of attention as potential markers for disease. Several epidemiological studies have reported platelet indices, in particular, the mean platelet volume (MPV), as markers for cardiovascular disease. Elevated MPV has been proposed as a risk factor for ischemic heart disease.^[10] High levels of MPV seem to be associated with acute myocardial infarction and mortality following myocardial infarction, suggesting that MPV is a potentially useful

prognostic biomarker in patients with cardiovascular disease.^[11] The mean platelet volume (MPV), platelet distribution width (PDW), and platelet crit (PCT) values exhibited significant variability. A significant inverse relationship was observed between parasitemia and PCT.^[12] Elevated Platelet size is also seen in individuals with hypertension and DM, both situations that influence the development of vascular disease.^[13] Since this is such a huge health problem in the community, the risk factors of stroke categorized as non-modifiable (age/gender/race) and modifiable (hypertension, smoking, alcohol, abdominal obesity, dietary habits) and increase in fibrinogen level and hyperhomocysteinemia and increase in MPV. It is in this context that this study has its significance. Platelets play important role in pathogenesis of atherosclerotic complication, contributory factor in thrombus formation.^[14]

However, the current knowledge of the usefulness of platelet indices as markers for adverse clinical outcomes in the elderly population is limited. The lack of data addressing this issue is somewhat surprising when one considers the relevant health,

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social, and economic implications of adverse clinical outcomes of elderly subjects and the need to identify risk factors at a stage of age-related decline that would be amenable to preventive interventions. In addition, the availability of powerful biological markers for clinical profile, hospitalization, and mortality would allow for an assessment of the efficacy of possible interventions. To address this issue, we have the plan to analyze the association of the following platelet indices with clinical profile in elderly subjects: Platelet distribution width (PDW), MPV, and platelet crit.

Materials and Methods

The prospective observational study was carried out from 2015 to 2017 at Acharya Vinoba Bhave Rural Hospital attached with Datta Meghe Institute of Medical Sciences (DU) Wardha, in central India. The patients were enrolled for the study after obtaining permission from the institutional ethics committee (Reg No. - DMIMS (DU)/IEC/2015-16/1489).

Recent or current infections, malignant disease, malnutrition, pharmacological interferences (antiplatelet drugs, immunosuppressive drugs, and antineoplastic drugs) were excluded from the study.

Sample size

The sample size was calculated based on the previous study where the proportion from the previous study was 28.5% and level of significance was 5%.^[15] The sample size for our study came out to be 905.66.

$$N = (z^2 / 2 \cdot p(1-p)) / d^2$$

$Z_{\alpha/2}$ = level of significance at 5% = 1.96

P = proportion from previous studies = 28.5% = 0.285

d = desired error of margin = 3% = 0.03

$$n = (1.96^2 \times 0.285(1-0.285)) / 0.03^2 = 905.66$$

The review was done regarding subjects' medical and pharmacological history, a physical examination. The disease status of the patient is based on the explicit diagnosis in the patient's medical history. Diseases that were considered in this study are hypertension, chronic obstructive pulmonary disease, ischemic heart disease and type II DM. Each participant's guardian received information about the purpose and objective of the study and signed an informed consent.

A total of 1060 patients were enrolled in the study of which 1000 patients were included, blood investigations were done and past history for the diseases considered for our study was taken. The inclusion is depicted in our flowchart [Figure 1].

Blood collection

Blood samples were obtained by venipuncture for biochemical analysis. The platelet indices were observed by the counter report from the central lab of the hospital. Following platelet indices were measured using automated hematology analyzer in the same laboratory (mean platelet volume and platelet distribution width and platelet crit).

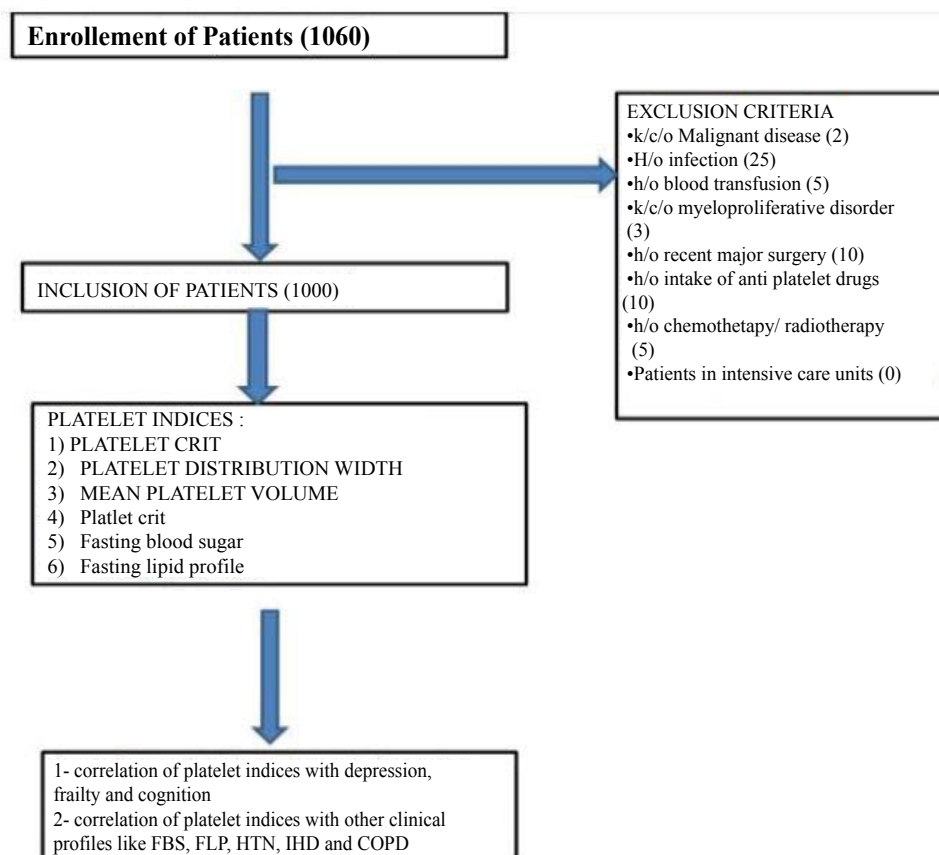


Figure 1: Flow chart showing the selection criteria.

Blood sugar measurement

The blood sugar level was measured by glucose oxidase and glucose peroxidase method. 1000 micro litre of reagent (glucose mono kit) had mixed with 10 microlitres of plasma, which was separated from the blood by centrifugation. Then half an hour after mixing readings was taken by using Robonic Semi Auto Analyzer. A fasting blood sugar sample was taken after 8 hours of overnight fasting. Sugar bulb was used for collection of the sample. The values will be expressed in gm/dl.

Fasting lipid profile measurement

Blood sample for a fasting lipid profile was collected in plane bulb after 8 hrs. Of fasting, the Randox Daytona analyzer was used to measure lipid profile (Triglyceride, High-density lipoprotein).

Lipid profile (Total cholesterol, HDL, triglycerides) was estimated by using the CODPOD method by Bayers kit. LDL was calculated using the Friedewald formula.

$$\text{LDL cholesterol} = (\text{Total cholesterol} - \text{HDL cholesterol} - \text{Triglycerides}/5)$$

The samples for fasting blood sugar and lipid profile were taken the early morning after a fasting period of 8 hours. The levels of the individual fraction of the lipid profile were interpreted in accordance with the range in central laboratory of our hospital as follows: Serum cholesterol: 120 – 200 mg/dl, HDL cholesterol: 35- 50 mg/dl, Serum triglycerides: 90 - 150 mg/dl, Serum LDL: 20 – 40 mg/dl, Serum VLDL: 90 – 165 mg/dl. The diagnosis of ischemic heart disease (IHD) will be done on the basis of history and ECG changes (New onset bundle branch block, Q waves, ST changes like T wave inversions, ST depression, and ST elevation) as per AHA guidelines.^[16]

The diagnosis of COPD was done on the basis of history and changes in Chest x-ray PA view like hyperinflation of lung fields, tubular heart, flattening of diaphragm.^[17]

Definitions

- **Plateletcrit:** It is a measure of total platelet mass (0.150 to 0.500%).
- **Mean platelet volume:** It is the average size of platelets (6.0 to 11.0/cu micrometer).
- **Platelet distribution width:** It is the variability in the size of the smallest and the largest platelets (11.0 to 18.0%).

Statistical analysis

Statistical analysis was done by using descriptive and inferential statistics using Chi-square test, Pearson’s correlation coefficient and software used in the analysis were SPSS 20.0 version, GraphPad Prism 6.0 version and p<0.05 is considered as the level of significance.

Observation and Results

In this study, we included 1000 patients of whom 601 (60.1%)

were males and 399 (39.9%) were females, mean age was 66.02 ± 5.76 years. We investigated for platelet indices, fasting blood sugar, and fasting lipid profile, blood pressures, ischemic heart disease and COPD in all the patients. The mean platelet crit 0.29 ± 0.17%, mean platelet volume was 9.25 ± 5.70 per μm³, and the mean platelet distribution width 14.18 ± 5.63%. There were 165 males who were chronic smokers and 107 males who were chronic alcoholics. Mean FBS was 121.84 ± 44.29 gm/dl, the mean total cholesterol was 85.34 ± 8.81 mg/dl, the mean HDL was 30.65 ± 3.66 mg/dl, the mean LDL was 36.52 ± 5.76 mg /dl, the mean VLDL was 18.16 ± 3.2 mg/dl, the mean triglyceride level was 184.11 ± 58.10 mg/dl, mean SBP was 117.78 ± 12.79 mm Hg, the mean DBP was 67.00 ± 10.60 mm Hg. There were 206 patients who were diagnosed as IHD and 245 patients who were diagnosed with COPD. All the baseline characteristics are shown in Table 1.

We compared the platelet indices with fasting blood sugar. The mean value of FBS was 121.84 gm/dl. All the platelet indices (platelet crit, MPV and PDW) showed negative correlation with FBS (r=-0.109, r=-0.105 and r=-0.128) respectively and it was statistically significant (p=0.001, p=0.0001 and p=0.0001) respectively. Thus the platelet indices decreased significantly with the increasing level of FBS [Table 2].

In our study the platelet indices showed positive correlation with SBP (r=0.027, r=0.027 and r=0.036) respectively but it was statistically not significant (p<0.05). This correlation is shown in Table 3.

Table 1: Baseline characteristics

Patient (n=1000)	Values (mean)	SD
Age (years)	66.02	± 5.76
Sex: Male	601 (60.1%)	
Female	399 (39.9%)	
Platelet count (lac/cu mm):	303210	± 21296
Platelet crit (%):	0.29	± 0.17
Mean platelet volume (μm ³)	9.25	± 5.70
Platelet distribution width (%):	14.18	± 5.63
FBS (gm/dl)	121.84	± 44.29
Total Cholesterol (mg/dl)	85.34	± 8.81
HDL (mg/dl)	30.65	± 3.66
LDL (mg/dl)	36.52	± 5.76
VLDL (mg/dl)	18.16	± 3.32
Triglyceride (mg/dl)	184.11	± 58.10
SBP (mm hg)	117.78	± 12.79
DBP (mm hg)	67.00	± 10.60

Table 2: Correlation of platelet indices with FBS.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.17	1000	-0.109	0.001,S
MPV	9.25	5.70	1000	-0.105	0.001,S
PDW	14.18	5.63	1000	-0.128	0.0001,S

Table 3: Correlation of platelet indices with SBP.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.17	1000	0.027	0.401,NS
MPV	9.25	5.70	1000	0.027	0.396,NS
PDW	14.18	5.63	1000	0.036	0.258,NS

The platelet indices showed positive correlation with DBP ($r=0.090$, $r=0.059$ and $r=0.084$) respectively, it was statistically significant for platelet indices such as (platelet crit and PDW) as $p=0.004$ and $p=0.008$ respectively but not for MPV ($p=0.064$). The correlation is shown in Table 4.

All the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.007$, $r=-0.011$ and $r=-0.022$ respectively) with total cholesterol and they were statistically not significant ($p=0.825$, $p=0.717$ and $p=0.491$ respectively). Thus the platelet indices decreased with the increasing level of TG but it was not significant. The correlation is shown in Table 5.

All the platelet indices had positive correlation ($r=0.036$, $r=0.039$ and $r=0.035$ respectively) with HDL and they were statistically not significant ($p=0.251$, $p=.216$ and $p=0.265$ respectively), the platelet indices increased with the increasing HDL but it was not significant. The correlation is shown in Table 6.

All the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.026$, $r=-0.028$ and $r=-0.041$ respectively) with LDL and they were statistically not significant ($p=0.408$, $p=.373$ and $p=0.193$ respectively). The platelet indices decreased with the increasing LDL but it was not significant. The correlation is shown in Table 7.

All the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.013$, $r=-0.025$ and $r=-0.025$ respectively) with VLDL and they were statistically not significant ($p=0.678$, $p=.434$ and $p=0.423$ respectively). The platelet indices decreased with the increasing VLDL but it was not significant. The correlation is shown in Table 8.

In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.115$, $r=-0.109$ and $r=-0.140$ respectively) with TG and they were statistically significant ($p=0.0001$, $p=0.001$ and $p=0.0001$ respectively). Thus the platelet indices decreased significantly with the increasing level of TG. The correlation is shown in Table 9.

In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.725$, $r=-0.766$ and $r=-0.731$ respectively) with IHD and they were statistically significant ($p=0.0001$, $p=.0001$ and $p=0.0001$ respectively). The mean value of Platelet indices were significantly higher for the patients with IHD than that of the patients without IHD ($p<0.001$). The correlation is shown in Table 10.

In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.796$, $r=-0.805$ and $r=-0.785$ respectively) with COPD and they were statistically significant ($p=0.0001$, $p=.0001$ and $p=0.0001$ respectively). All the mean value of the parameters related to Platelet indices were significantly higher for the patients with COPD than that of the patients without COPD ($p<0.001$). The correlation is shown in Table 11.

Discussion

In our study, there was an association of the Platelet indices like platelet distribution width (PDW), MPV, and platelet crit with clinical profile in elderly subjects.

We compared the platelet indices with fasting blood sugar. The mean value of FBS was 121.84 gm/dl. All the platelet indices (platelet crit, MPV and PDW) showed negative correlation

Table 4: Correlation of platelet indices with DBP.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.17	1000	0.090	0.004,S
MPV	9.25	5.70	1000	0.059	0.064,NS
PDW	14.18	5.63	1000	0.084	0.008,S

Table 5: Correlation of platelet indices with TC.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.179	1000	-0.007	0.825,NS
MPV	9.25	5.704	1000	-0.011	0.717,NS
PDW	14.18	5.631	1000	-0.022	0.491,NS

Table 6: Correlation of platelet indices with HDL.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.179	1000	0.036	0.251,NS
MPV	9.25	5.704	1000	0.039	0.216,NS
PDW	14.18	5.631	1000	0.035	0.265,NS

Table 7: Correlation of platelet indices with LDL.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.179	1000	-0.026	0.408,NS
MPV	9.25	5.704	1000	-0.028	0.373,NS
PDW	14.18	5.631	1000	-0.041	0.193,NS

Table 8: Correlation of platelet indices with VLDL.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.17	1000	-0.013	0.678,NS
MPV	9.25	5.70	1000	-0.025	0.434,NS
PDW	14.18	5.63	1000	-0.025	0.423,NS

Table 9: Correlation of platelet indices with TG.

Platelet indices	Mean	Std. Deviation	N	Correlation 'r'	p-value
Platelet Crit	0.29	0.17	1000	-0.115	0.0001,S
MPV	9.25	5.70	1000	-0.109	0.001,S
PDW	14.18	5.63	1000	-0.140	0.0001,S

Table 10: Correlation of platelet indices with IHD.

Platelet indices	Mean	Std. Deviation	N	Correlation 'p'	p-value
Platelet Crit	0.29	0.17	1000	-0.725	0.0001,S
MPV	9.25	5.70	1000	-0.766	0.0001,S
PDW	14.18	5.63	1000	-0.731	0.0001,S

Table 11: Correlation of platelet indices with COPD.

Platelet indices	Mean	Std. Deviation	N	Correlation 'p'	p-value
Platelet Crit	0.29	0.17	1000	-0.796	0.0001,S
MPV	9.25	5.70	1000	-0.805	0.0001,S
PDW	14.18	5.63	1000	-0.785	0.0001,S

with FBS. ($r=-0.109$, $r=-0.105$ and $r=-0.128$) respectively and it was statistically significant ($p=0.001$, $p=0.0001$ and $p=0.0001$) respectively. In a study by Zuberi B F et al. [18] the difference of MPV among the non-DM and DM groups was significant with p-value of 0.0001 and 95% CI of -1.03 and -0.38. The difference between the non-DM and IFG group was significant with p-value of 0.03 and 95% CI of -0.67 and -0.02. The difference in MPV was significant between IFG and DM groups with p-value of 0.26 and 95% CI of -0.68 and -0.03. In a study by Farah Jabeen et al. [19] the positive association between glycemic control determinant (FBG and HbA1c) and platelet indices indicate the clinical usefulness of HbA1c level and platelet indices hence surrogate markers in early detection of diabetic complications. Masanori Shimodaira et al. [20] showed MPV of the pre-diabetic group was higher than in other groups. MPV was independently and positively associated with FPG, in pre-diabetic subjects and also in normal FPG subjects ($\beta=0.020$ and $\beta=0.006$, respectively).

In our study the platelet indices (platelet crit, MPV and PDW) showed positive correlation with SBP ($r=0.027$, $r=0.027$ and $r=0.036$) respectively but it was statistically not significant ($p<0.05$). In a study by Xia Cao et al. [21] it showed that MPV is associated with prehypertension. After controlling for the main potential confounders (age, sex, and BMI), and for other potentially relevant variables (smoking and serum cholesterol), high levels of MPV were associated with greater odds of prehypertension.

In our study the platelet indices (platelet crit, MPV and PDW) showed positive correlation with DBP ($r=0.090$, $r=0.059$ and $r=0.084$) respectively, it was statistically significant for all platelet indices (platelet crit and PDW) as $p=0.004$ and $p=0.008$ respectively but not for MPV ($p=0.064$).

In a study Kun Yang, et al. [22] MPV was negatively associated with DBP in male, PDW had a negative association with SBP. PLT was associated with male's DBP.

All the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.007$, $r=-0.011$ and $r=-0.022$ respectively) with total cholesterol and they were statistically not significant ($p=0.632$, $p=0.825$, $p=0.717$ and $p=0.491$ respectively).

Contrasting results were found in a study Y.-L. Chang et al. [23] in which patients with higher platelet count had higher TC values (210 ± 40 mg/dl) while patients with lower platelet count showed lower TC values (193.9 ± 37.5 mg/dl). The study had no data for other platelet indices that we have examined like PCT, PDW, and MPV.

In our study all the platelet indices (platelet crit, MPV and PDW) had positive correlation ($r=0.036$, $r=0.039$ and $r=0.035$ respectively) with HDL and they were statistically not significant ($p=0.251$, $p=0.216$ and $p=0.265$ respectively). Contrasting results were found in a study Y.-L. Chang et al. [23] which showed patients with higher platelet count had higher HDL values (46.6 ± 015.3 mg/dl) and patients with lower platelet count showed lower HDL values (45.4 ± 12.8 mg/dl).

In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.026$, $r=-0.028$ and $r=-0.041$ respectively) with LDL and they were statistically not significant ($p=0.408$, $p=0.373$ and $p=0.193$ respectively). Contrasting results were found in a study Y.-L. Chang et al. [23] which revealed patients with higher platelet count had higher LDL values (137.8 ± 35.7 mg/dl) and patients with lower platelet count showed lower LDL values (127 ± 33.2 mg/dl). In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.013$, $r=-0.025$ and $r=-0.025$ respectively) with VLDL and they were statistically not significant ($p=0.678$, $p=0.434$ and $p=0.423$ respectively). In our study, however, there was a negative correlation of VLDL with platelet indices and it was statistically not significant ($p>0.05$). In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.115$, $r=-0.109$ and $r=-0.140$ respectively) with TG and they were statistically significant ($p=0.0001$, $p=0.001$ and $p=0.0001$ respectively).

In our study all the platelet indices (platelet crit, MPV and PDW) had negative correlation ($r=-0.725$, $r=-0.766$ and $r=-0.731$ respectively) with IHD and they were statistically significant ($p=0.0001$, $p=0.0001$ and $p=0.0001$ respectively).

In a study by Sravan K Reddy et al. [24] which showed significantly higher MPV in patients with STEMI (10.2 ± 2.8) as compared to controls (8.5 ± 6.9). PDW was also significantly higher in cases compared to controls ($p<0.05$). This difference could be due to the patient's age group which was above 60 years in our study and also as in Sravan K Reddy et al. the enrolled patients were on an antiplatelet drug which could have altered the platelet indices whereas in our study we had excluded those individuals who were on antiplatelet drugs. Lippi G et al. [25] showed analysis of MPV values in 2304 adult patients admitted for provisional diagnosis of Acute Coronary Syndrome. They found all those patients, having cardiac troponin T levels of 0.03 ng/mL or greater and ischemic electrocardiographic changes, had higher MPV values than non-ACS patients who had normal cardiac troponin T levels.

In our study all the platelet indices (plateletcrit, MPV and PDW) had negative correlation ($r=-0.796$, $r=-0.805$ and $r=-0.785$ respectively) with COPD and they were statistically significant ($p=0.0001$, $p=0.0001$ and $p=0.0001$ respectively). In a study by Sevinc S. Ulasli et al. [26] they included 47 patients with COPD and showed MPV values were 9.3 ± 1.4 and 8.6 ± 1.0 fl during stable period and during acute exacerbation, respectively. The MPV values were significantly lower in patients during acute exacerbation than in those during the stable period of COPD and in control subjects (both, $P<0.001$). The results suggest that assessment of MPV in COPD exacerbation may indicate systemic inflammation. The results were similar to that in our study. In a study by Makhlof et al. [27] different result was seen compared to our study. Mean Platelet volume (MPV), Platelet distribution width (PDW), Platelet crit (PCT) were significantly higher in COPD patients. There was no significant difference in the various laboratory data among different stages of COPD ($P>0.05$). In COPD patients, MPV was a significantly positively

correlated with CRP and PDW ($r=0.346$, $P<0.001$; $r=0.510$, $P<0.001$ respectively) and negatively correlated with the platelet count ($r=-0.294$, $P=0.002$).

Some diets and nutrients have been shown to affect platelet function. Dark chocolate, foods with low glycemic index, garlic, ginger, omega-3 PUFA, onion, purple grape juice, tomato, and wine reduce platelet aggregation. Dark chocolate also reduces P-selectin expression, PAC-1 binding, and platelet microparticle formation. Berries inhibit platelet function (PFA-100 assay). Energy drinks have been shown to increase platelet aggregation and caffeine increases platelet microparticle formation.^[28] Plant foods can provide α -linolenic acid but are devoid of the long-chain omega-3 fatty acids—eicosapentenoic acid and docosahexenoic acid. A significant rise in platelet linoleic acid concentration and a decline in platelet arachidonic acid (AA) concentration were observed in vegetarians. We could not find any article correlating diets and platelet indices.^[28]

Conclusion

Among the clinical parameter, patients with higher FBS had decreased platelet crit, PDW, and MPV. Also patients with higher platelet indices had higher systolic and diastolic blood pressure. Patients with fasting lipid profile when compared with platelet indices showed no significant correlation except for triglyceride levels. All the platelet indices showed significant correlation with IHD and COPD, which were lower in patients with the respective diseases.

Conflict of Interest

I declare there is no conflict of interest

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