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Original Article

The relationship between mean platelet volume and albuminuria in patients with type 2 diabetes mellitus

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ABSTRACT

Background&aim: Mean platelet volume (MPV) is suggested as a marker of platelet reactivity and tendency for thrombosis and microvascular complications like albuminuria in patients with type 2 DM. We aimed to measure the MPV in patients with type 2 DM and its correlation with albuminuria, body mass index (BMI), duration of DM, hypertension (HTN), stroke, ischemic heart disease (IHD), and HbA1c level.
Methods: A cross sectional study included 100 patients with type 2 DM ≥ 18 y of both genders who were randomly selected from the medical units of Baghdad Teaching Hospital. After taking verbal consents; MPV was measured&correlated with aimed variables. Diabetics with HbA1c ≤ 7% were considered as having adequate control while those with (HbA1c) > 7% as having poor control. Albumin creatinine ratio (ACR) in urine was measured and classified into normal, moderately and severely increased. Odds ratios with 95% CI were calculated and P ≤ 0.05 was considered as statistically significant.
Results: The mean MPV was 7.7 fl ± 1.2. Regarding ACR, 42% had normal level, 37% with moderately increased and 21% had severely increased level. Regarding HbA1c, 68% were having poorly controlled DM. Mean platelets' count and MPV were higher in the uncontrolled group with a statistically significant association. There was a statistically significant positive correlation between MPV and albuminuria, duration of DM, HTN, IHD, Stroke, BMI, HbA1c, and platelets count.
Conclusions: The mean MPV was statistically significantly higher in the uncontrolled DM group and there was a statistically significant positive correlation between MPV and albuminuria.

1. Introduction

DM has been considered as a 'prothrombotic state'. It is considered as the most common acquired thrombophilia because of the existing dysfunction of hemostasis. Platelets are thought to be a central element of the atherothrombotic process due to their prothrombotic and proinflammatory functions [1]. Platelets from subjects with diabetes show hyper-reactivity which may play a pivotal role in the development of diabetic complications [2]. MPV is a reliable index of platelet size, it correlates well with the functional status of platelets and their activation. Larger platelets with higher MPV are hemostatically more reactive and produce higher amounts of the prothrombotic factor thromboxane A2, increasing a propensity to thrombosis [3]. Patients with DMT2, are exposed to the increased platelet reactivity due to metabolic (e.g. hyperglycemia, hypertriglyceridemia) and systemic abnormalities (e.g. oxidative stress, inflammation) and insulin resistance [4]. The use of most parameters of platelet activity as biomarkers of diabetic thrombocytopathy is time-consuming, expensive, and requires specialty training [1,5]. While MPV is a simple, quick and easy-to-measure parameter of platelet size, and of its prothrombotic potential. It can be determined by routine automated hemograms at a low cost [6].

It has been found in multiple researches that MPV is significantly higher in DMT2 patients having micro-vascular complications than in patients without them [7]. It is well known that HbA1c, should be kept below 7% in order to reduce the risk of

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micro-vascular and macro-vascular complications in DMT2 patients [8]. It has been suggested that improved glycemic control decreases MPV and thereby, reduced platelet activity by proper glycemic control may prevent or delay vascular complications in these patients [9].

In the approximately 40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay. Albuminuria in the range of 30–300 mg/24 h is called *moderately increased albuminuria.* Patients with small increase in albuminuria increase their levels of urinary albumin excretion, typically reaching dipstick positive levels of proteinuria (>300 mg albuminuria) 5–10 years after the onset of early albuminuria. *Moderately increased albuminuria* is a potent risk factor for cardiovascular events and death in patients with type 2 DM and from the earliest stages of *moderately increased albuminuria*, it usually takes 10–20 years to reach end stage renal disease (ESRD) [10]. A few researches have suggested a relationship between MPV and albuminuria and the results were conflicting [11].

A study that was held at university of Sarajevo in Bosnia and Herzegovina by (Kadić D. et al., 2016) concluded that MPV correlates with glycemic control markers in DMT2 patients [12]. In another two researches that were done by (Kodiatte TA. et al., 2012) [13] and (Dyal A. et al., 2016) [14]; both concluded that MPV was found to be higher in subjects with Type-2 DM and significantly increased in diabetics with poor glycemic control and having a longer duration of diabetes. Another study done in Turkey by (Kurt H. et al., 2017) concluded that both the diabetic and prediabetes group had higher MPV values compared to the non-diabetic group [15].

2. Aim of study

In this study, our aim was to measure the MPV in patients with type 2 DM and to find its correlation with the presence of albuminuria. We also studied the correlation of MPV with other parameters like duration of DM, BMI, random blood sugar (RBS), HTN, stroke, IHD, and HbA1c level as an indicator of glycemic control.

3. Patients and methods

3.1. Study design and sample

This was a cross-sectional descriptive study which included patients who were admitted to the inpatient medical units of Baghdad Teaching Hospital/Medical City/Iraq from June 2018 till December 2018.

3.2. Inclusion criteria were

A Total of 100 adult patients with type 2 DM; who were ≥18 years of either gender was selected randomly and included in the study.

3.3. Exclusion criteria were

1. Acute severe infectious or inflammatory disease.
2. Acute coronary syndrome.
3. Chronic liver dysfunction.
4. Severe renal insufficiency.
5. Patients using anti-platelet agents.
6. Patients with anemia.
7. Patients receiving chemotherapy.

Verbal consents were taken from all study sample. Data was collected by standard questionnaire about name, gender, age, duration of DM, presence of hypertension, and IHD, history of stroke. A blood sample was obtained and sent for mean platelet volume, platelets count, RBS, and HbA1c. A urine sample was taken for measuring albumin creatinine ratio. Detailed physical examination was done and BMI was calculated.

3.4. Definitions

- ***Hypertension:***Is considered if the recorded systolic blood pressure ≥140 mmHg and or diastolic blood pressure ≥90 mmHg, or if the patient was on current antihypertensive therapy [16].
- ***Diabetes mellitus:***Is defined as the use of insulin or glucose-lowering medication on admission, or a diet for diabetes documented in medical history. The diagnosis of "undiagnosed DM" was made if patients with fasting glucose >7.0 mmol/L or random glucose >11.1 mmol/L together with an admission HbA1c >6.5% according to the latest American Diabetes Association (ADA) recommendations [17].
- ***Albuminuria:***Is defined as ACR of 30–300 mg/g which was considered as moderately increased albuminuria, and more than 300 mg/g was considered as severely increased proteinuria [18], according to the following table:

Albuminuria categories in CKD

Category	ACR (mg/g)	Terms
A1	< 30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	> 300	Severely increased**

*Relative to young adult level. **ACR 30-300 mg/g for > 3 months indicates CKD.
**Including nephrotic syndrome (albumin excretion ACR > 2220 mg/g)

- ***BMI:***Is equal tokg/m^2 where kg is a person's weight in kilograms and m^2 is their height in meters squared. A BMI ≥25.0 is considered as overweight, while the healthy range is from 18.5 to 24.9 [19].
- ***Ischemic Heart Disease:***The presence of angiographically proven coronary artery stenosis, history of myocardial infarction or coronary artery bypass grafting operation and presence of current myocardial ischemia by ischemic changes indicated electrocardiography [20].
- ***Stroke:***is defined as an imaging evidence of brain ischemia for both ischemic and hemorrhagic strokes, or appropriate clinical scenario for transient ischemic attack [21].

3.5. Procedure and measurements

A random urine sample was collected using sterile containers and a kit was used to measure albumin in urine and measured by Biomax device in the lab. All patients were tested by drawing a blood sample under aseptic technique for the following:

- **MPV and platelets count;** were measured as part of CBC using venous blood sample with EDTA anticoagulation. The reference range of MPV was determined according the hospital's laboratory reference which was from 6 to 10 fl.
- **Glycosylated hemoglobin (HbA1c)** level was measured regardless of whether they had been fasting, by a spectrophotometer. Type 2 diabetic patients with (HbA1C) ≤ 7% were considered as having adequate glycemic control while those with (HbA1C) > 7% were considered as having poor glycemic control according to the latest ADA guidelines [22]. Also; **RBS** was measured from the drawn blood sample. The study protocol

was approved by the ethical committee of the Council of Arab-Board of Health Specialization (Medicine).

3.6. Statistical analysis

Statistical package for Social Sciences (SPSS version 20) was used for data analysis, and Microsoft Excel to generate graphs. Continuous variables were expressed as a mean ± standard deviation (SD), while categorical variables were expressed as frequency and percentages. For bivariate analysis, the student's test (*t*-test) was used to compare means of continuous variables, and Pearson's Chi square to compare the categorical variables. Bivariate logistic regression test was used to evaluate the significant association between MPV and covariates. Odds ratios (OR) with 95% confidence interval (CI) were calculated from this test. The statistical tests were two-sided, and a P-value ≤0.05 was considered statistically significant.

Table 1
Demographic, Clinical and laboratory characteristics of the sample.

Characteristic (Sample = 100)	No.	Percentage
Age, years (mean ± SD[a])	57.55 ± 9.91	
Gender, No		
Male	40	40%
Female	60	60%
Hypertension:		
Hypertensive	58	58%
Non-hypertensive	42	42%
Ischemic heart disease:		
Present	35	35%
Absent	65	65%
Duration of diabetes		
mean ± SD (years)	5.75 ± 3.39	
Stroke:		
Present	29	29%
Absent	71	71%
BMI[b] (kg/m^2)		
<18	0	0%
18.5–24.9	5	5%
≥25	95	95%
MPV[c], mean ± SD (fl)	7.7 ± 1.2	
Random blood sugar, mean ± SD (mg/dl)	265 ± 86	
Platelets count/cm^2		
(mean ± SD)	269.6 ± 70.3	
Albuminuria mg/g		
<30	42	42%
30–300	37	37%
>300	21	21%
HbA1C %		
≤7	32	32%
>7	68	68%

[a] Standard deviation.
[b] Body mass index.
[c] Mean platelet volume.

4. Results

Table 1 demonstrated demographic, Clinical and laboratory characteristics of the studysample. The mean age of the sample was 57.55 years ±9.91 and 40 (40%) patients were males. The mean duration of DM was 15.42 years ±7.61. Out of 100 patients; there were 58 (58%) hypertensive patients, 65 (65%) with history of IHD, 71 (71%) with history of stroke. Regarding BMI, none of the patients had a BMI <18.5 kg/m^2, 5 (5%) patients were having a BMI between 18.5 and 24.9 kg/m^2 and 95 (95%) patients were having a BMI of 25 kg/m^2 and higher. The mean MPV for the sample was 7.7 fl ± 1.2 and the mean platelets count was 269.6/cm^2 ± 70.3. The level of albuminuria was as follows: 42 (42%) patients were having <30 mg/g which was considered as normal or mildly increased, 37 (37%) patients had a level between 30 and 300 mg/g which was considered as moderately increased and 21 (21%) patients were having a level of >300 mg/g which was considered as severely increased albuminuria. Regarding HbA1c, 32 (32%) patients were having controlled glycemia (≤7%) and 68 (68%) patients were belonging to the uncontrolled glycemia group (>7%).

Table 2 demonstrated that from patients with no history of IHD; there were 37 (37%) patients with poor glycemic control and from those with history of IHD; there were 31 (31%) patients with poor control. There was a statistically significant association between IHD and glycemic control (p-value 0.001).

About history of stroke, for patients with no history of stroke; there were 32 patients with good glycemic control versus 39 with poor control and for patients with history of stroke; there were no patients with good glycemic control and 29 patients with poor control. There was a statistically significant association between stroke and glycemic control (p-value 0.005). Regarding patients with average BMI (18.5–24.9 kg/m^2); there was 1 patient with good glycemic control and 4 patients with poorly controlled diabetes.

For patients with BMI ≥25 kg/m^2; there was 31 patients with well controlled diabetes versus 64 with poor control. There was a statistically significant association between BMI and glycemic

Table 2
Clinical and laboratory characteristics of the controlled and uncontrolled DM groups.

Characteristics		HbA1c		P-value
		≤7Count (%)	>7Count (%)	
IHD[a]	No IHD	28 (28%)	37 (37%)	0.001
	IHD	4 (4%)	31 (31%)	
Stroke	No Stroke	32 (32%)	39 (39%)	0.005
	Stroke	0	29 (29%)	
BMI[b]	<18.5	0	0	0.001
	18.5–24.9	1 1 (%)	4 (4%)	
	≥25	31 (31%)	64 (46%)	
Albuminuria (mg/g)	<30	26 (26%)	16 (16%)	0.001
	30–300	6 (6%)	31 (31%)	
	>300	0	21 (21%)	
Platelets count (/cm^2)		Mean ± SD[c] 222.41 ± 39.3	Mean ± SD 291.85 ± 70.93	0.005
Random blood sugar (mg/dl)		226.56 ± 67.8	283.09 ± 84.6	0.001
Mean platelet volume (fl)		6.9 ± 1	8.1 ± 1.1	0.001

[a] Ischemic heart disease.
[b] Body mass index.
[c] Standard deviation.

Table 3
Pearson's correlation between mean platelet volume (MPV) and other variables.

dMPV	Albuminuria	Age	Duration of DM	HTN[a]	IHD[b]	Stroke	BMI[c]	HbA1c	Platelets count	RBS[d]
Correlation	0.580	0.209	0.426	0.248	0.534	0.279	0.328	0.358	0.282	0.472
P-Value	0.001	0.037	0.001	0.013	0.001	0.005	0.001	0.001	0.005	0.001

[a] Hypertension.
[b] Ischemic heart disease.
[c] Body mass index.
[d] Random blood sugar.

control (p-value 0.001). Regarding the level of albuminuria; for those with ACR<30 mg/g, there were 26 patients with well controlled diabetes versus 16 patients with poorly controlled disease. For ACR between 30 and 300 mg/g there were 6 patients with good glycemic control compared to 31 patients with poor control. For ACR level >300 mg/g, all the 21 patients had poorly controlled diabetes. There was a statistically significant association between the level of albuminuria and glycemic control (p-value 0.001).

The mean platelet count for the controlled diabetes group was $222.41 \pm 39.3/cm^2$ and for the uncontrolled group was $291.85 \pm 70.93/cm^2$ with a statistically significant association (p-value 0.005). The mean RBS for the controlled diabetes group was 226.5 ± 676.8 mg/dl, whereas the mean RBS was 283.09 ± 84.6 mg/dl for the uncontrolled group, with a statistically significant association (p-value 0.001). The mean MPV for the controlled diabetes group was 6.9± 1 fl, whereas the mean MPV was 8.1 ± 1.1 fl for the uncontrolled group, with a statistically significant association (p-value 0.001).

Table 3 illustrated that according to Pearson's correlation; there was a statistically significant positive correlations between MPV and albuminuria, duration of diabetes, HTN, IHD, Stroke, BMI, HbA1c, platelets count and RBS. On the other hand; there was no statistically significant correlation with age.

Table 4 illustrates that for patients with albuminuria of <30 mg/g, the mean MPV was 6.6 ± 0.9 fl in the controlled diabetes group and 7.7 ± 1.0 fl for the uncontrolled group. While for the patients with albuminuria of 30–300 mg/g, the mean MPV was 8 ± 0.0 fl for the controlled diabetes group and 7.8 ± 1.1 fl for the uncontrolled group. Whereas regarding patients with albuminuria of >300 mg/g, there was nil patient in controlled diabetes group while the mean MPV was 8.9 ± 0.9 fl for the uncontrolled group. There was a statistically significant association between the mean MPV and the level of albuminuria according to HbA1c with p-value 0.001.

Fig. 1 shows that with increasing degree of albuminuria; the mean MPV increases to 8.9 ± 0.9 fl in patients with severely increased albuminuria and the association was statistically significant (p-value 0.001).

Fig. 2 shows that the mean MPV was higher in the uncontrolled diabetes group (about 8 ± 0.0 fl) and the association was statistically significant (p-value 0.001).

Fig. 3 shows that the mean MPV was higher in the hypertensive group (about 8.1 ± 1.0 fl) and the association was statistically significant (p-value 0.013).

Fig. 4 demonstrates that the mean MPV was higher in the IHD positive group (about 8.6 ± 1.0 fl) and the association was statistically significant (p-value 0.001).

Fig. 5 demonstrates that the mean MPV was higher (about 8.2 ± 1.0 fl) in the stroke group and the association was statistically significant (p-value 0.005).

Fig. 6 demonstrates that the mean MPV(about 8.2 ± 1.3 fl) was higher in the average BMI group and the association was statistically significant (p-value 0.001).

Fig. 7 demonstrates that there was no statistically significant association between MPV and gender (p-value 0.148).

Table 4
The association between mean MPV and albuminuria according to glycemic control.

	Albuminuria (mg/g)						P-value
	>300 HbA1c		30–300 HbA1c		<30 HbA1c		
	>7	≤7	>7	≤7	>7	≤7	
	Mean ± SD[a]						
MPV[b] (fl)	8.9 ± 0.9	0.0	7.8 ± 1.1	8.0 ± 0.0	7.7 ± 1.0	6.6 ± 0.9	0.001

[a] Standard deviation.
[b] Mean platelet volume.

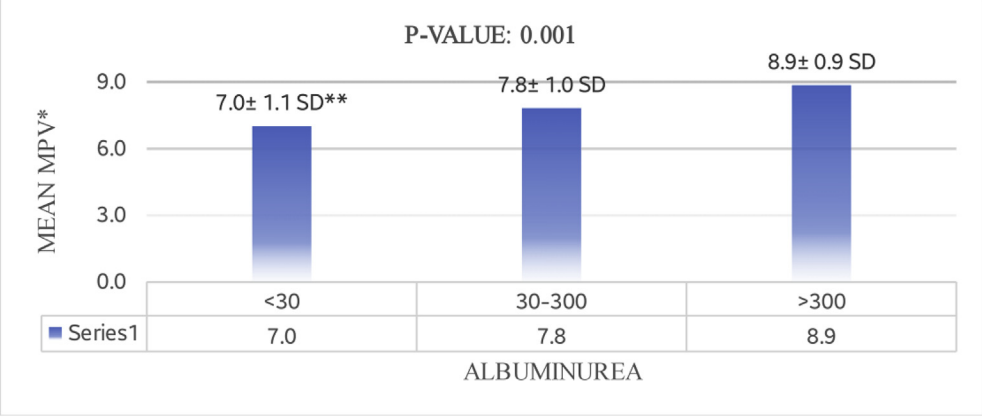

Fig. 1. A simple histogram of the association of mean MPV and albuminuria. *: Mean platelet volume, **: Standard deviation.

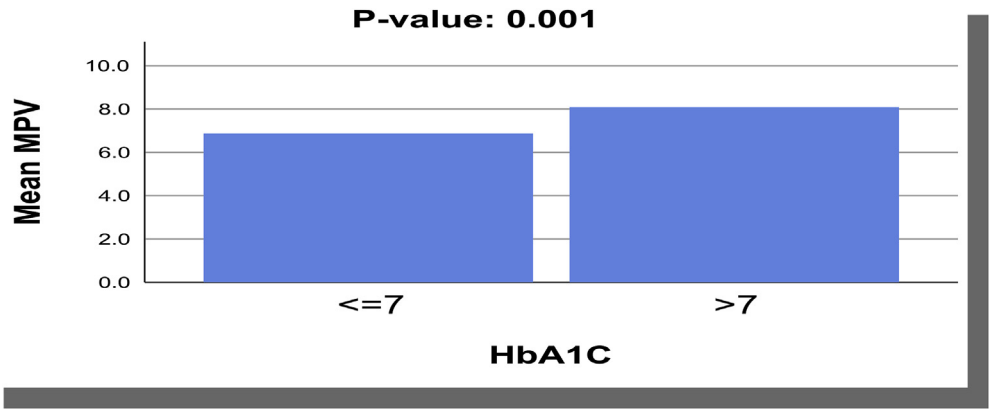

Fig. 2. A simple histogram of association of mean MPV by HbA1c.

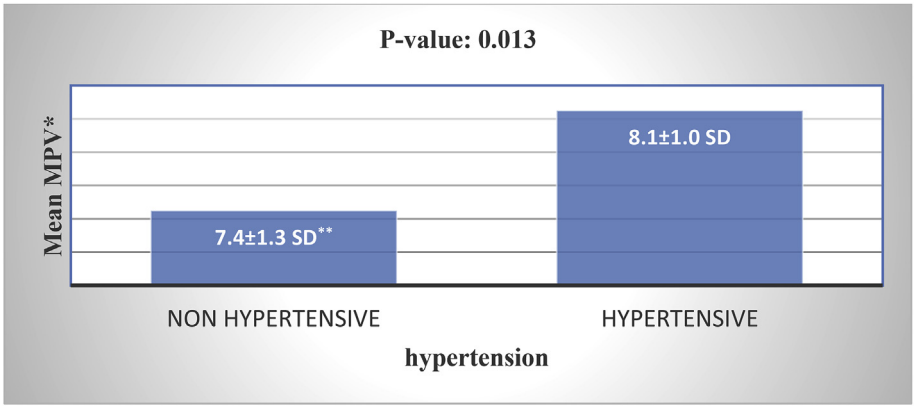

Fig. 3. A simple histogram of association of mean MPV and Hypertension, *: Mean platelet volume, **: Standard deviation.

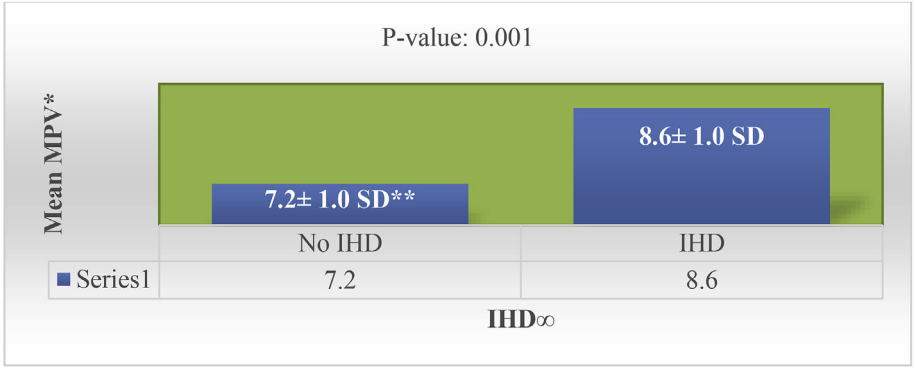

Fig. 4. A simple histogram of association of mean MPV and IHD, *: Mean platelet volume, **: Standard deviation,∞: Ischemic heart disease.

5. Discussion

The present study was conducted to measure the MPV in patients with type 2 DM and to study its correlation with the presence of albuminuria. We also studied the correlation of MPV with other parameters like duration of DM, RBS, HTN, history of stroke and IHD, and with HbA1c level as an indicator of diabetes control.

In our study; the mean age of the sample (100 adults) was 57.55 years ±9.91, while in studies that were held at University of Sarajevo in Bosnia and Herzegovina by (Kadić D. et al., 2016) [12], the mean age was 62.24 ± 11.86 years and in another study that was conducted by (Yenigun EC. et al., 2014) [23], the mean age was 59.35 ± 9.04 years. The number of males and females were close to those both studies.

The frequency of hypertension was higher in our study than in a study conducted by (Virgin Joena M. et al., 2017) [24]. The frequency of IHD and stroke were close to the results of the study done in Turkey by (Yenigun EC. et al., 2014) [23], and another in India by (Archana A. et al., 2016) [25].

In our study; the duration of DM was shorter than the study by (Kadić D. et al., 2016) [12] and close to a study done in India by (Dubey I. et al., 2017) [26]. The mean BMI was higher in our study in comparison with the study held in Pakistan by (Muhammad I. et al., 2015) [27]. This may be explained by the different lifestyle and the

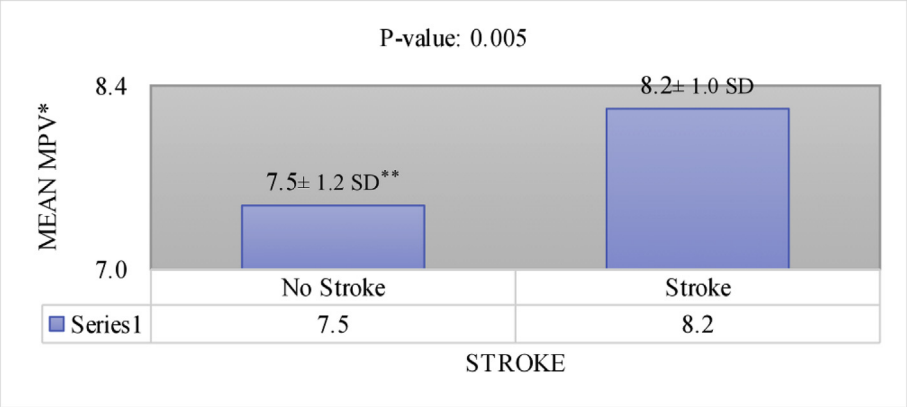

Fig. 5. A simple histogram of association of mean MPV and Stroke, *: Mean platelet volume, **: Standard deviation.

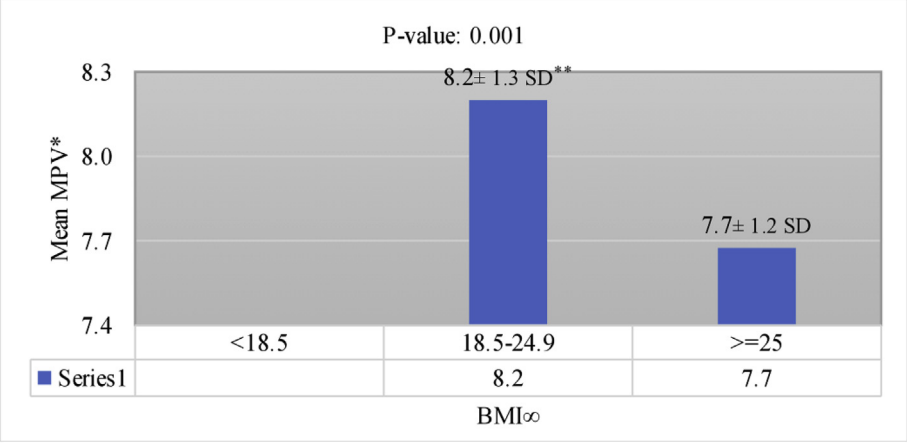

Fig. 6. A simple histogram of association of mean MPV and BMI, *: Mean platelet volume, **: Standard deviation, ∞: Body mass index.

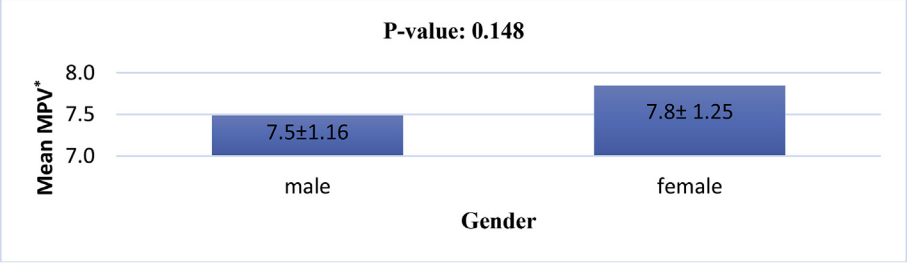

Fig. 7. A simple histogram of mean MPV and gender, *: Mean platelet volume.

tendency to have poorly controlled diabetes in our study.

The MPV was similar in our study to the result of the study conducted in India by (Joena M V. et al., 2017) [24] but lower than mean MPV in a study done in China by (Chen X. et al., 2017) [28] and another study by (Rajagopal RL. et al., 2018) [29].

In our study, the frequency of nephropathy (albuminuria), was higher than in a study by (Kadić D. et al., 2016) [12]. This may be explained by the higher percentage of patients with poorly controlled DM in our study, and maybe the delay in diagnosis, non-compliance with treatment and delay in seeking medical advice by the patients.

Regarding the characteristics of controlled and uncontrolled diabetic's groups, the association with gender was not statistically significant and this goes with the study by (Yenigun EC. et al., 2014) [23], and a study by (Rajagopal RL. et al., 2018) [29].

While the association with age was statistically significant and this was against the results of the study by (Kadić D. et al., 2016) [12]. The uncontrolled DM group has higher mean age and this means more comorbidities and less compliance with medications and so worse control of DM.

The mean platelets count was higher in the uncontrolled DM group and this goes with a study by (Swaminathan A. et al., 2016) [30].

In our study, the duration of DM was higher in the uncontrolled group, this goes with the results of a study by (Dindar S. et al., 2013) [31] and against the results of the studies by (Dubey I. et al., 2017)

[26] and (Muhammad I. et al., 2015) [27], this may be due to the fact that longer duration of DM in our study results in more complications.

In our study, the mean BMI was higher in the uncontrolled DM group, this is against the results of (Dindar S. et al., 2013) [31]. This may be explained by the different lifestyle and the higher number of patients with poorly controlled diabetes in our study.

The mean MPV in this study was significantly higher in the uncontrolled group and this goes with results of the studies by (Dubey I. et al., 2017) [26] (Rajagopal L. et al., 2018), [29] (Swaminathan A. et al., 2016), [30], and (Dindar S. et al., 2013) [31].

In our study, the frequencies of HTN, IHD, and stroke; were higher in the uncontrolled diabetic group and the association was a statistically significant.

There was a statistically significant positive correlation between MPV and albuminuria, BMI, RBS, HbA1c. This goes with the results of the studies done by (Alhadas K. et al., 2016) [32], (Hasan Z. et al., 2016) [33], and (Akinsegun A. et al., 2014) [34].

In our study, there was a statistically significant negative correlation between MPV and age, this goes with the result of a study by (Hasan Z. et al., 20160) [33].

In our study, there was a negative correlation between MPV and age and there was no statistically significant association between MPV and gender, this goes with the result of a study by (Hasan Z. et al, 20160 [33].

6. Conclusions

1 The mean MPV was statistically significantly higher in the uncontrolled DM group.
2 There was a statistically significant positive correlation between mean MPV and albuminuria.

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