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Differential Association of Platelet Indices with Macrovascular versus Microvascular Complications in Patients with Type 2 Diabetes Mellitus.

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Abstract

Background: Elevated platelet reactivity plays a key role in the pathogenesis of vascular complications in T2DM patients, via creating a prothrombotic state. Platelet indices reflect variation in size and heterogeneity, which may be used as an indirect measure of reactivity of platelets, offering potential as cost-effective biomarkers for risk of vascular complications. Nowadays, the commonly available automated cell counters in most hospitals provide Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet-Large Cell Ratio (PLCR), Platelet-Large Cell Count (PLCC), Platelet Count (PLT), and Plateletcrit (PCT), along with the complete blood cell counts (CBC). This study investigated the association of these platelet indices with clinically manifested vascular complications in T2DM patients. ***Methods:*** T2DM patients aged 25–75 years were enrolled from outpatient clinics and inpatient wards of the department of general medicine from a tertiary care hospital. Sociodemographic profiles, duration of disease, and the presence of vascular complications were carefully documented. Venous blood samples were collected in EDTA tubes and analyzed within two hours using the same automated cell counter (Mindray BC-5800) providing comprehensive platelet indices. The primary objective was to determine the association between various platelet indices and clinically manifested vascular complications in T2DM patients. The secondary objective was to explore the differences in platelet indices between the subsets of T2DM patients with only macrovascular versus T2DM patients with only microvascular complications. Associations of various variables were analyzed using Mann-Whitney test, independent t-test, Chi-Square test, and Fisher's exact test, according to the type of variable and the normality of data. ***Results:*** A total of 50 T2DM patients who had no clinically manifested vascular complications were enrolled in one group (group A), and a total of 50 patients who had manifested any one or more vascular complications were enrolled in the second group (group B). In group B, 34 patients had manifested only macrovascular complications (group B1); 9 patients had manifested only microvascular complications (group B2); and 7 patients had manifested both macrovascular and microvascular complications. Only PDW was significantly higher in T2DM patients with any one or more clinically manifested vascular complications versus T2DM patients without any clinically manifested vascular complications (p=0.034), while the differences in MPV, PLCR, PLCC, PLT, and PCT did not reach statistical significance between the two groups. Furthermore, MPV, PDW, and PLCR were significantly high in T2DM patients who had manifested only macrovascular complications as compared to T2DM patients who had manifested only microvascular complications, with p values 0.009, 0.047 and 0.011, respectively. ***Conclusion:*** The elevated platelet size has a stronger association with the macrovascular complications as compared to microvascular complications in T2DM patients, indirectly indicating higher platelet reactivity in this patient population. Prospective studies are warranted to examine the cause-and-effect relationship between large platelets and macrovascular complications in T2DM patients.

Keywords: Type 2 Diabetes Mellitus; Vascular complications of Diabetes; Platelet Reactivity; Mean Platelet Volume; Platelet Distribution Width; Platelet Large Cell Ratio.

INTRODUCTION

Platelets are now recognized as playing roles in multiple physiological and pathological processes, including hemostasis and thrombosis, vasoconstriction, neovascularization, inflammation, immunity, atherosclerosis, and tumor growth [1,2]. However, hemostasis and thrombosis are considered the primary physiological and pathological functions of platelets, respectively. Both processes begin with platelet activation, followed by platelet aggregation, and culminate in clot

formation. This prothrombotic function of platelets is particularly relevant in diabetes mellitus (DM), where platelet hyperreactivity may be a significant factor contributing to the increased risk of vascular complications [3-6].

The complications of DM are usually grouped as nonvascular (e.g., infections) and vascular based on their pathophysiology. Among the vascular complications, retinopathy, neuropathy, and nephropathy are the three key microvascular complications, resulting from altered endothelial structure and cellular function. These are specific to diabetes mellitus, and long-standing hyperglycemia is the primary causative factor. On the other hand, Coronary Heart Disease (CHD), Cerebro Vascular Disease (CVD), and Peripheral Artery Disease (PAD) are the three key macrovascular complications. These are not specific to diabetes mellitus, but they occur at a significantly higher rate in diabetic individuals as compared to the general population. Insulin resistance and related dyslipidemia are considered as the primary causative factor for development of macrovascular complications in diabetes mellitus, instead of chronic hyperglycemia [7–12].

Type 2 Diabetes Mellitus (T2DM) constitutes a significant global health burden due to its high prevalence and the high morbidity and mortality associated with its complications. This chronic metabolic disorder, characterized by relative insulin deficiency (insulin resistance), often progresses silently, with many patients being diagnosed only after the onset of various complications, contributing to substantial health and economic burdens [13,14]. A measure of platelet reactivity in T2DM patients can guide clinicians to prognosticate the risk of vascular complications.

Platelet reactivity can be determined by a change in the level of platelet activity in response to a stimulus. A diverse array of methodologies exists for assessing platelet activity, each with unique advantages and limitations. Platelet Count (PLT) and Bleeding Time (BT) are simple methods, widely used by clinicians. Complex methods like platelet aggregometry, and flow cytometry are mostly limited to research work. Light transmission platelet aggregometry (LTA) measures light transmission in platelet rich plasma and is considered gold standard, but it is labor intensive. Several methods have been used to develop point-of-care testing systems. Platelet Function Analyzer (PFA-100; Innovance PFA-200) measures platelet-dependent primary hemostasis by simulating platelet adhesion and aggregation under high shear-stress blood flow conditions and provides a Closure Time (CT) in seconds. Multiple Electrode Aggregometry (MEA) measures whole blood electrical impedance [15,16]. VerifyNow system is turbidimetry based measurement of platelet aggregation, after stimulating with agonist in whole blood [17]. Plateletworks counts platelets before and after aggregation in whole blood [18].
A simpler method to indirectly estimate platelet reactivity is to measure platelet size and heterogeneity. Numerous studies have demonstrated a correlation between platelet size and platelet function, with larger platelets showing increased thrombotic potential compared to their smaller counterparts. These larger platelets are generally considered to possess enhanced functional activity and, consequently, a higher potential for thrombogenesis. Historically, it was posited that increased platelet size reflects a population of younger, more reactive platelets. However, this relationship remains a topic of debate. While elevated platelet turnover does result in a greater average platelet size and a higher proportion of immature (reticulated) platelets, such associations are not observed under steady-state conditions of thrombopoiesis and platelet clearance. The presence of residual RNA serves as a marker for reticulated platelets (young or immature platelets), and both large and reticulated platelets tend to contain higher RNA content and exhibit heightened activity. Although large platelets often include a greater percentage of reticulated platelets, it is important to note that reticulated platelets can also be small in size. This complexity complicates the direct association between platelet size and age. Therefore, it appears that platelet size and platelet age represent two distinct, yet interrelated, determinants of platelet functional capacity, each governed by separate physiological mechanisms [19–23].

Nowadays, the commonly available automated cell counters in most hospitals provide various platelet indices along with the complete blood cell counts (CBC). Mean Platelet Volume (MPV) reflects average platelet size. Platelet Distribution Width (PDW) measures the variability in platelet size and is indicative of platelet heterogeneity. Platelet Large Cell Ratio (PLCR) indicates the proportion of large platelets (>12 fL), while Platelet Large Cell Count (PLCC) provides an absolute count of these large platelets. Platelet Count (PLT) remains a fundamental measure, offering a direct estimate of platelet availability in circulation. Plateletcrit (PCT) reflects the total platelet mass in the blood and serves as a composite marker integrating both platelet size and count, offering insights into overall thrombopoietic activity [24–29]. While advanced tests for platelet reactivity are more costly and complex, platelet indices are a simpler and cheaper alternative way for indirectly measuring platelet reactivity. They can be easily obtained with routine CBC, making them practical for widespread clinical applications.

Decreased MPV has been observed with increased disease activity in ulcerative colitis [30], disease exacerbation in rheumatoid arthritis [31], Crohn's disease [32], active systemic lupus erythematosus patients in adults [33], neuroendocrine tumor of pancreas compared to adenocarcinoma of pancreas [34], and uterine cervical cancer [35]. On the other hand, increased MPV has been observed with myocardial infarction [36], stroke [37], chronic sinusitis [38], gastric carcinoma [39], pancreatic cancer [40], and colorectal cancer [41].

Several studies have reported elevated MPV in T2DM patients compared to healthy controls [42–44]. Jindal et al observed significantly higher values of MPV, PDW, and PLCR in T2DM patients compared to non-diabetic controls [45]. However, these findings are not universally consistent. For instance, Giovanetti et al found no significant differences in platelet indices (MPV, PDW, and PCT) between diabetic and non-diabetic individuals in a cohort of 306 subjects [46]. Similarly, a study conducted on 100 T2DM patients in Nigeria reported lower MPV levels in diabetic patients compared to controls [47].

Moreover, numerous investigations have explored the association between platelet indices and the presence of vascular complications in T2DM. Nevertheless, the literature remains inconclusive, with studies reporting inconsistent results regarding these relationships [43-45,48,49].

This study aimed to investigate the potential association between various platelet indices and the presence of clinically manifested (overt) vascular complications in T2DM patients. It also sought to explore differences in platelet indices between subsets of T2DM patients manifesting isolated macrovascular complications versus T2DM patients manifesting isolated microvascular complications, without overlap.

MATERIALS AND METHODS

This is a cross-sectional, observational study conducted at the tertiary care hospital of the Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, in Northern India. The period of study was from May 2017 through April 2018. T2DM patients were enrolled from the outpatient and inpatient units of the Department of General Medicine of the hospital, by simple random method. Inclusion criteria included patients diagnosed with T2DM; and ability to understand and speak English and/or Hindi. Patients with ages below 25 years; ages above 75 years; critical illness; or inability to communicate were excluded from this study.

The study protocol was reviewed and approved by the Institutional Review Board. This research was conducted in accordance with the ethical principles of the Declaration of Helsinki. Prior to enrollment, all participants received a detailed information sheet outlining the study's objectives and procedures, and written informed consent was obtained from each subject.

Patients were interviewed face-to-face, regarding the overt manifestation of any of the vascular complications of T2DM, namely, CHD, CVD, PAD, Retinopathy, Neuropathy and Nephropathy, and the responses were documented along with the sociodemographic details. Duration of disease (Time since diagnosis of T2DM) was noted in years. Interval between diagnosis of T2DM and occurrence of complication was noted in years. Detailed physical examination was done to look for signs of vascular complications related to diabetes. Body Mass Index (BMI) was calculated in Kilogram per square meter. Medical records and relevant investigations were reviewed to confirm the presence or absence of overt vascular complications. Most recent fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) and glycated hemoglobin (A1C) were noted.

Venous samples from the subjects were collected in EDTA tubes. Samples were analyzed within 2 hours using the same automated cell counter (Mindray, Model BC-5800). Automated reports were collected, including MPV, PDW, PLCC, PLCR, PLT, PCT, Total Leukocyte Count (TLC), Neutrophil -to-Lymphocyte ratio (NLR), Red Blood Cell Count (RBC Count), Hematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red Cell Distribution Width – Standard Deviation (RDW-SD).

The primary objective was to compare the various platelet indices in T2DM patients who had clinically manifested any one or more vascular complications versus those T2DM patients who had not clinically manifested any vascular complications. The secondary objective was to compare the platelet indices in the T2DM patients who had clinically manifested any one or more macrovascular complications but none of the microvascular complications versus those T2DM patients who had clinically manifested any one or more microvascular complications but none of the macrovascular complications.

No formal sample size calculation was attempted as the study population was restricted to one single facility. Patient enrollment was stopped when a sample size of 50 patients was achieved in each group. Data were collected in paper format and later entered in the Microsoft Excel spreadsheet, and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, Version 25.0. The categorical variables were presented in the form of number and percentage (%), and the quantitative data were presented as mean ± SD and/or as median with interquartile range (25th-75th percentiles). The data normality was checked by using the Shapiro-Wilk test. Platelet indices were found to have non-normal distribution. Therefore, the association between various platelet indices and vascular complications was analyzed using the Mann-Whitney test. The variables which were quantitative and

normally distributed in nature were analyzed using the independent t-test. The association of the variables which were qualitative in nature was analyzed using the Chi-Square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. Spearman rank correlation coefficient was used for correlation of platelet indices with each other and with various other variables. The p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 patients were enrolled in the group of T2DM patients without any clinically manifested vascular complications (Group A, n = 50), and a total of 50 patients were enrolled in the group of T2DM patients who had clinically manifested any one or more of the vascular complications (Group B, n = 50), constituting a total study population of 100 patients. In group B, patients have manifested at least one vascular complication in isolation, or more than one vascular complication in various overlaps. Out of the 50 patients, 31 had CHD, 11 had CVD, 3 had PAD, 4 had retinopathy, 8 had neuropathy, and 8 had nephropathy.

Among patients who had overlap of more than one vascular complication, 1 patient had retinopathy, neuropathy and nephropathy (diabetic triopathy). 1 patient had retinopathy and neuropathy. 1 patient had CHD and nephropathy; 1 patient had CHD, CVD and nephropathy; 1 patient had CHD, CVD, retinopathy, and nephropathy; 1 patient had CHD and nephropathy; 1 patient had CHD and neuropathy; 2 patients had CHD, PAD and neuropathy Of the 50 T2DM patients in Group B, those who had manifested one or more macrovascular complications without any accompanying microvascular complications were categorized as Group B1 (n = 34). Conversely, patients who had manifested one or more microvascular complications without any macrovascular complications were categorized as Group B2 (n = 9). Seven patients who exhibited both macrovascular and microvascular complications were excluded from the analysis addressing the secondary objective. This stratification enabled a focused evaluation of platelet parameters in relation to specific vascular complication profiles among T2DM patients.

The demographic and clinical characteristics of the study participants are summarized in Table 1. The median age was 5 years higher in group B (61.5 years [55–66.75]) as compared to group A (56.5 years [45.25–65]) (p = 0.039). Among the subgroups, patients in Group B2 (only microvascular complications) were significantly older than those in Group B1 (only macrovascular complications) (p = 0.033).

The duration of diabetes was 2 years longer in Group B (5 years) compared to Group A (3 years) (p=0.042), Moreover, a significant difference in disease duration was also noted between Group B1 and Group B2 (p=0.001), indicating longer disease duration in those with microvascular involvement. In group B, 13 T2DM patients out of 50 had manifested one or more vascular complications at the time of diagnosis of T2DM. The median interval between diagnosis of T2DM and occurrence of vascular complications was 1.25 years [0-5] in group B1 versus 7 years [4-9] in group B2, although the difference was statistically not significant.

44% (n=22) patients had a positive family history of T2DM in group B as compared to 28% (n=14) in group A (p=0.096). 41.18% (n=14) had a positive family history of T2DM in group B1 as compared to 33.33% (n=3) in group B2 (p=0.035). HTN was the most common comorbidity in group A (40%, n=20) as well as in group B (46%, n=23). Other comorbidities were infrequent and not significantly different (all p > 0.05). Other comorbidities in group A included 3 Chronic Obstructive Pulmonary Disease (COPD), 4 Hypothyroidism, 2 Tuberculosis, 1 chronic HCV infection, 1 chronic HBV infection, 1 rheumatic heart disease, 1 osteoarthritis, 1 cholelithiasis, and 1 infertility. Other comorbidities in group B included 3 COPD, 1 Hypothyroidism, 1 angioedema, 1 anemia, 1 alcohol use disorder, 1 glaucoma, 1 hemorrhoids, and 1 Prolapse Inter-Vertebral Disc (PIVD). 38% (n=19) patients had no comorbidities in group A comparable to 38% (n=19) in group B (p=0.439). There were no statistically significant differences between groups with respect to gender distribution, BMI, comorbid HTN, FPG, 2-h PG, and A1C. Blood cell counts of the study population are depicted in Table 2. Both the groups were comparable in terms of TLC and NLR. RBC count was lower in group B compared to group A (p=0.008). RDW-SD was higher in group B vs group A (p =0.001).

Comparison of platelet indices is depicted in Table 3. PDW was significantly higher in T2DM patients who had clinically manifested any one or more vascular complications (group B) as compared to those T2DM patients who had not manifested any overt vascular complications (group A) (p=0.034). MPV and the median PLCR (p=0.208) also trended higher in group B compared to group A, although this difference did not reach statistical significance (p = 0.305 and 0.208, respectively). PLCC showed no significant differences between groups A and B (p=0.896). On the other hand, PLT and PCT trended lower in group B as compared to group A, but again the difference was statistically not significant.

T2DM patients who had manifested any one or more macrovascular complications and none of the microvascular complications (group B1) had higher MPV, PDW and PLCR as compared to the those T2DM patients who had manifested any one or more microvascular complications and none of the macrovascular complications (group B2) with p values,

0.009, 0.047, and 0.011 respectively. PLCC was also higher in group B1 compared to group B2, but the difference was statistically non-significant. On the other hand, PLT and PCT were lower in group B1 compared to group B2, but the difference was statistically non-significant.

Table 4 shows the correlation-coefficients (r) and corresponding p-values between platelet indices and various demographic and clinical parameters in T2DM patients. BMI showed a significant positive correlation with MPV (r = 0.243, p = 0.015), PLCC (r = 0.218, p = 0.029), and PLCR (r = 0.229, p = 0.022). This indicates that individuals with higher BMI tended to have larger and more heterogeneous platelets. No significant correlations were observed between platelet parameters and age, duration of diabetes, interval between diagnosis of T2DM and onset of vascular complications, most recent FPG, 2-h PG, or A1C.

Table 5 summarizes the correlation-coefficients (r) and corresponding p-values between platelet indices and other blood cell counts. A significant positive correlation was observed between TLC and both PLT (r = 0.311, p = 0.002) and PCT (r = 0.255, p = 0.011). Conversely, TLC showed a negative association with MPV (r = –0.237, p = 0.018), PDW (r = –0.313, p = 0.002), and PLCR (r = –0.273, p = 0.006). MCV correlated positively with MPV (r = 0.302, p = 0.002), PDW (r = 0.377, p < 0.001), and PLCR (r = 0.239, p = 0.017). A weak positive correlation was noted between PDW and RDW-SD (r = 0.211, p = 0.035). No significant associations were found between NLR and platelet indices.

A detailed correlation analysis among various platelet indices revealed several significant interrelationships (Table 6). MPV demonstrated a strong positive correlation with PLCR (r = 0.984, p < 0.0001) and a moderate positive correlation with PDW (r = 0.422, p = 0.002) and PLCC (r = 0.293, p = 0.039). Conversely, MPV was inversely correlated with PLT (r = –0.542, p = 0.0001) and PCT (r = –0.164, p = 0.253; not significant). These findings highlight the inverse relationship between platelet size parameters (MPV, PDW, PLCR) and platelet count (PLT) as well as platelet mass (PCT). PLCC demonstrated a strong positive correlation with PLT and PCT; it also demonstrated a weak positive correlation with MPV and PLCR, and a weak negative correlation with PDW.

Table 1: Comparison of baseline characteristics of study population between T2DM without and with vascular complications.

Baseline characteristics of study population	T2DM without vascular complications (Group A, n=50)	T2DM with vascular complications (Group B, n=50)	p value A vs B	T2DM with only macrovascular complications (group B-1, n=34)	T2DM with only microvascular complications (group B-2, n=9)	p value B1 vs B2
Age (years)	56.5(45.25-65)	61.5(55-66.75)	0.039*	60(53-65)	62(56-63)	0.033*
Female	23 (46%)	22 (44%)	0.841†	14 (41.18%)	3 (33.33%)	0.253§
Male	27 (54%)	28 (56%)		20 (58.82%)	6 (66.67%)	
Family history of T2DM	14 (28%)	22 (44%)	0.096†	14 (41.18%)	3 (33.33%)	0.035§
BMI	22.08 ± 3.21	21.79 ± 3.72	0.681‡	21.66 ± 3.78	22.36 ± 3.88	0.770‡
Duration of disease (years)	3(1-6)	5(2.5-10)	0.042*	4(2.5-6)	8(7-10)	0.001*
Interval between diagnosis of T2DM and occurrence of vascular complications (years)	-	4(0.021-7)	NA	1.25(0-5)	7(4-9)	0.065*
Comorbid Hypertension	20 (40%)	23 (46%)	0.545†	13 (38.24%)	6 (66.67%)	0.439§
No comorbidities	19 (38%)	19 (38%)	1†	16 (47.06%)	2 (22.22%)	0.402§
FPG (mg/dL)	152(136-194.75)	171(143.5-211.5)	0.164*	168(149-191)	224(158-224)	0.913*
2-h PG (mg/dL)	196(181-225)	194.5(181-243)	0.836*	191(179-218.5)	243(184-243)	0.652*
A1C (%)	8.15(7.8-8.675)	8.4(7.825-9.375)	0.313*	8.15(7.825-8.75)	9.8(8.4-9.9)	0.714*

‡ **Independent t test,** * **Mann Whitney test,** § **Fisher's exact test,** † **Chi square test**

Table 2: Comparison of Blood Cell Counts of study population between T2DM without and with vascular complications.

CBC	T2DM without vascular complications (Group A, n=50)	T2DM with vascular complications (Group B, n=50)	p value A vs B	T2DM with only macrovascular complications (Group B1, n=34)	T2DM with only microvascular complications (Group B2, n=9)	p value B1 Vs B2
TLC ($\times10^9$/L)	9.11(7.12-11.52)	8.41(6.855-10.695)	0.345*	8.54(6.542-11.192)	8.68(7.05-9.59)	0.87*
NLR	2.12(1.584-3.482)	2.15(1.652-3.873)	0.591*	2.13(1.652-3.824)	2.63(1.928-4.228)	0.403*
RBC Count ($\times10^{12}$/L)	4.68(4.048-5.038)	4.16(3.88-4.755)	0.008*	4.16(3.888-4.808)	4.6(4.06-4.64)	0.676*
HCT (%)	40.6(36.425-44.275)	38.3(34.875-42.4)	0.123*	38.7(35.25-42.4)	39.9(36.5-43.3)	0.72*
MCV (fL)	87.45(83.725-93.375)	91.6(86.225-94.15)	0.078*	91.6(85.25-94.35)	90(85.3-92.9)	0.502*
MCH (pg)	27.7(26.225-29.125)	28.35(26.8-29.9)	0.166*	28.2(26.725-30.05)	28.3(26.3-29.8)	0.905*
MCHC (g/dL)	31.48 ± 1.21	31.35 ± 1.19	0.612‡	31.25 ± 1.26	31.94 ± 0.8	0.123‡
RDW-SD (fL)	48(44.175-49.7)	51.4(48-55.775)	0.001*	51.6(48.425-56.1)	48(42.8-52.4)	0.071*

‡ Independent t test, * Mann Whitney test

Table 3: Comparison of platelet indices between T2DM without and with vascular complications.

Platelet indices	T2DM without vascular complications (Group A, n=50)	T2DM with vascular complications (Group B, n=50)	p value A vs B	T2DM with only macrovascular complications (Group B1, n=34)	T2DM with only microvascular complications (Group B2, n=9)	p value B1 vs B2
MPV (fL)	9.79 ± 1.44	10.12 ± 1.71	0.305‡	10.28 ± 1.64	8.7 ± 1.04	0.009‡
PDW (fL)	16.5 (15.925-16.8)	16.65 (16.4-17.175)	0.034*	16.7 (16.5-17.45)	16.4 (16.2-16.5)	0.047*
PLCR (%)	37.85 (29.075-45.525)	39.1 (30.65-52.925)	0.208*	47.05 (32.95-52.925)	30.8 (24.8-33.1)	0.011*
PLCC ($\times10^9$/L)	83 (68.25-93.75)	83 (54.75-102.5)	0.896*	77.5 (48.5-104.5)	63 (54-84)	0.429*
PLT ($\times10^9$/L)	230.5 (166.5-301)	195.5 (164-268.25)	0.197*	176.5 (120.25-258.25)	270 (204-273)	0.128*
PCT (%)	0.22 (0.189-0.267)	0.21 (0.154-0.255)	0.245*	0.19 (0.138-0.258)	0.21 (0.155-0.249)	0.601*

‡ Independent t test, * Mann Whitney test

Table 4: Correlation of platelet indices with baseline characteristics.

Variables		Age (years)	BMI	Duration of disease (years)	Interval between diagnosis of T2DM and occurrence of vascular complications (years)	FPG (mg/dL)	2-h PG (mg/dL)	A1C (%)
MPV (fL)	r	-0.179	0.243	0.052	-0.056	-0.151	-0.024	0.018
	P value	0.074	0.015	0.608	0.697	0.134	0.813	0.862
PDW (fL)	r	-0.06	0.088	0.006	-0.166	-0.032	0.032	0.048
	P value	0.551	0.383	0.949	0.248	0.755	0.754	0.638
PLCR (%)	r	-0.186	0.229	0.042	-0.071	-0.151	-0.044	0.015
	P value	0.064	0.022	0.681	0.621	0.133	0.664	0.885
PLCC ($\times10^9$/L)	r	-0.057	0.218	0.06	0.091	0.001	-0.006	0.078
	P value	0.57	0.029	0.552	0.529	0.99	0.953	0.44
PLT ($\times10^9$/L)	r	0.076	-0.019	-0.001	0.204	0.129	0.056	0.062
	P value	0.453	0.852	0.991	0.155	0.2	0.578	0.539
PCT (%)	r	0.015	0.081	0.02	0.205	0.094	0.063	0.065
	P value	0.885	0.423	0.84	0.153	0.353	0.536	0.518

Spearman rank correlation coefficient

Table 5: Correlation of platelet indices with blood cell counts.

Variables		TLC ($\times10^9$/L)	NLR	RBC Count ($\times10^{12}$/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW-SD (fL)
MPV (fL)	r	-0.237	-0.127	-0.004	0.172	0.302	0.246	-0.209	0.061
	P value	0.018	0.208	0.966	0.087	0.002	0.014	0.037	0.545
PDW (fL)	r	-0.313	0.001	0.038	0.269	0.377	0.394	0.095	0.211
	P value	0.002	0.995	0.705	0.007	0	0	0.349	0.035
PLCR (%)	r	-0.273	-0.132	0.036	0.167	0.239	0.167	-0.254	0.097
	P value	0.006	0.189	0.72	0.097	0.017	0.097	0.011	0.338
PLCC ($\times10^9$/L)	r	0.069	-0.215	0.003	-0.058	0.045	-0.056	-0.24	-0.083
	P value	0.497	0.032	0.974	0.567	0.655	0.577	0.016	0.413
PLT ($\times10^9$/L)	r	0.311	-0.046	-0.067	-0.239	-0.191	-0.232	0.011	-0.166
	P value	0.002	0.646	0.509	0.017	0.058	0.02	0.915	0.099
PCT (%)	r	0.255	-0.129	-0.044	-0.173	-0.09	-0.161	-0.104	-0.143
	P value	0.011	0.199	0.664	0.085	0.371	0.109	0.303	0.156

Spearman rank correlation coefficient

Table 6: Correlation of platelet indices with each other.

Variables	MPV (fL)	PDW (fL)	PLCR (%)	PLCC ($\times10^9$/L)	PLT ($\times10^9$/L)	PCT (%)
MPV (fL)						
r	–	0.422	0.984	0.293	-0.542	-0.164
P value	–	0.002	<0.0001	0.039	0.0001	0.253
PDW (fL)						
r	–	–	0.471	-0.159	-0.574	-0.436
P value	–	–	0.001	0.270	<0.0001	0.002
PLCR (%)						
r	–	–	–	0.292	-0.569	-0.188
P value	–	–	–	0.040	<0.0001	0.189
PLCC($\times10^9$/L)						
r	–	–	–	–	0.555	0.845
P value	–	–	–	–	<0.0001	<0.0001
PLT ($\times10^9$/L)						
r	–	–	–	–	–	0.888
P value	–	–	–	–	–	<0.0001
PCT (%)						
r	–	–	–	–	–	–
P value	–	–	–	–	–	–

Spearman rank correlation coefficient

DISCUSSION

In this study, PDW was found to be significantly higher in T2DM patients with clinically manifested vascular complications (Group B) compared to T2DM patients who have not clinically manifested any vascular complications (Group A). In contrast, no statistically significant differences were observed between the two groups for other platelet indices, including MPV, PLCR, PLCC, PLT, and PCT. However, both the mean MPV and the median PLCR demonstrated a non-significant trend toward higher values in T2DM patients with vascular complications, suggesting a potential increase in platelet size and heterogeneity within this subgroup.

Kodiatte et al have also reported non-significantly higher MPV associated with complications in T2DM patients [48]. Similarly, Shilpi et al reported non-significantly higher MPV, PDW, and PLCR in T2DM patients with vascular complications versus T2DM patients without vascular complications [50]. Both these studies have included T2DM patients with hypertension, hypercholesterolemia, hypertriglyceridemia, in the group with vascular complications, which are common comorbid conditions associated with T2DM, but are not typically considered as vascular complications. Therefore, the difference in platelet size and heterogeneity between the two groups may have been diluted. A previous study by Demirtunc et al involving 70 T2DM patients from Turkey did not find a correlation between MPV and diabetic vascular complications [44]. Similarly, another Turkish study of 140 T2DM patients reported that MPV levels were significantly higher in diabetics compared to 40 healthy controls; however, MPV did not correlate with the stages of diabetic retinopathy. Additionally, there were no significant differences in PDW and PCT between diabetics, diabetic retinopathy patients, and healthy controls [49]. In contrast, a study from Indonesia found significantly higher MPV and PDW in T2DM patients with vascular complications compared to those without vascular complications [51], highlighting possible differences attributable to population characteristics and/or methodological variations across studies.

Furthermore, a notable finding of this study was that MPV, PDW, and PLCR were significantly higher among T2DM patients who had manifested any one or more macrovascular complications but none of the microvascular complications (Group B1), compared to those T2DM patients who had manifested any one or more microvascular complications but none of the macrovascular complications (Group B2). These results indicate that larger platelets are more strongly associated with macrovascular complications than with microvascular complications in T2DM patients. Furthermore, the findings imply that there is either a relatively weaker association or no notable association between increased platelet size and microvascular complications in T2DM patients. The identification of distinct platelet phenotypes further underscores the heterogeneity within the T2DM population, with subgroups of patients exhibiting variations in platelet size that indirectly reflect differing levels of platelet reactivity.

These findings are in conformation with the established concept that macrovascular complications in T2DM are primarily manifested as acute thrombotic events, like acute coronary syndrome, ischemic stroke, and acute limb ischemia and are likely to express higher platelet reactivity, and therefore larger platelet size. In contrast, microvascular complications are a result of cumulative cellular damage due to chronic glycemic load. Therefore, in the natural history of T2DM patients it takes a longer duration to manifest a microvascular complication (about 5 to 20 years) [7–12]. The hemorrhagic stroke is an exception. It is conventionally listed as a macrovascular complication of T2DM, but the underlying mechanism of hemorrhagic stroke is microvascular pathology. In contrast, Jindal et al reported significantly higher PDW in T2DM patients with any one or more microvascular complications versus T2DM patients without any vascular complications, while MPV and PLCR were non-significantly elevated in the microvascular complication group [45]. Buch et al reported a significantly higher MPV in diabetics with complications versus diabetics without complications. Buch et al also reported significant correlation of MPV with microvascular complications, and non-significant elevation of MPV with macrovascular complications, and no significant correlation of PLCR with any diabetic vascular complications [52]. Another study on 352 T2DM patients from Northeast Ethiopia reported significantly higher MPV, PDW, and P-LCR in T2DM patients with microvascular complications [53]. These studies have not ruled out the presence of macrovascular complications, in the patient population manifesting microvascular complications.

Hence, the results may have been confounded by the presence of macrovascular complications. This study did not stratify participants based on confounding factors, like smoking and antiplatelet drugs, which could influence platelet indices and the incidence of vascular complications. The sample size may have limited the power to detect significant differences in small groups. Because of the cross-sectional design of this study as well as most other contemporary studies on platelet indices, it is not possible to ascertain whether the platelet size increases in response to the acute thrombotic events in these patients, or whether these patients were carrying larger platelets at baseline and the acute thrombotic events were precipitated at a higher incidence due to the higher levels of platelet reactivity associated with larger platelets. These findings of single center studies may have been affected by characteristics of study population and cannot be widely generalized to all populations. In addition, there are many methodological differences in various studies. Therefore, longitudinal studies with large cohorts and standardized methodology are warranted to examine the cause-and-effect relationship between large platelets and macrovascular complications or acute thrombotic events in T2DM patients.

CONCLUSION

This study demonstrates that the T2DM patients who had clinically manifested vascular complications exhibit significantly elevated PDW as compared to those T2DM patients who had not clinically manifested any vascular complications, while the differences in MPV, PLCR, PLCC, PLT, and PCT between the two groups were statistically non-significant. Further, MPV, PDW, and PLCR were significantly higher in those T2DM patients who had manifested only macrovascular complications as compared to those T2DM patients who had manifested only microvascular complications, while the differences in PLCC, PLT and PCT were statistically non-significant. These findings suggest that elevated platelet size has a stronger association with macrovascular complications as compared to microvascular complications in T2DM patients. To strengthen these observations, further research should involve larger cohorts and adopt a prospective study-design

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Conflicts of Interest

The authors declare they have no financial or non-financial competing interests to disclose.

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