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ORIGINAL ARTICLE

Positive Relationship of Platelet Volume Indices with HbA1c in Unselected Type-2 Diabetes Mellitus Patients

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SUMMARY

Background: **The aim of this study is to investigate the relationship of several platelet volume indices with glycated hemoglobin (HbA1c) in a large cohort of type 2 diabetes mellitus (T2DM) patients.**
Methods: **This is a retrospective study conducted on 1,729 T2DM patients. The database was based on the laboratory information system of the Department of Clinical Laboratory Medicine of the First Affiliated Hospital of Shaoyang University from May 2017 to February 2018. These patients were divided into two subgroups depending on their platelet volume indices and HbA1c levels.**
Results: **Mean platelet volume (MPV), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were positively correlated with HbA1c levels (all $p < 0.01$), but not the thrombocytocrit (PCT). The platelet, MPV, PDW, P-LCR, and glucose levels were significantly higher in the higher HbA1c subgroup (≥ 6.5%) than that in lower subgroup (< 6.5%) ($p < 0.01$). The platelet, MPV, P-LCR, PCT, HbA1c, and glucose levels were significantly higher in higher PDW subgroup (≥ 17 fL) than that in lower subgroup (< 17 fL) ($p < 0.01$). In the higher MPV subgroup (≥ 12 fL), the platelet, PDW, P-LCR, PCT, HbA1c, and glucose levels were significantly higher than that in lower subgroup (< 12 fL) ($p < 0.01$).**
Conclusions: **These platelet volume indices were positively correlated with HbA1c in T2DM patients, which might provide potential new parameters to monitor glucose control.**
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KEY WORDS

HbA1c, mean platelet volume, thrombocytocrit, platelet-large cell ratio, platelet distribution width

INTRODUCTION

Diabetes mellitus (DM) is the most challenging metabolic problem in the world. The incidence of type 2 diabetes mellitus (T2DM) in constantly increasing, which accounts for over 80% of cases in DM. The worldwide prevalence of this condition among adults has been estimated to increase by more than 50% in the next two decades, i.e., from 285 million adults in 2010 to 439 million adults by 2030 [1].
The measurement of glycated hemoglobin (HbA1c) has now been established as an essential criterion for diagnosing DM in the general population [2]. It is less vul-

nerable to pre-analytical factors with a much lower biological variability and is less influenced by acute stress and conventional drugs which may impair glucose metabolism [3].

DM is considered as a "prothrombotic state" owing to sustained hyperglycemia, dyslipidemia, and insulin resistance. Increased platelet activity plays a major role in the development of vascular complications in DM [4]. Although there are several measurements to show the platelet activity (platelet aggregometry, platelet surface p-selectin, platelet surface-activated glycoprotein IIb/IIIa), almost all of these measurements are time-consuming, expensive or requiring special training [5]. Among different platelet morphological indices, high mean platelet volume (MPV) and platelet distribution width (PDW) of peripheral platelets is considered a marker associated with increased platelet activity *in vivo*, mainly related to the larger volume of newly-released platelets which display an increased pro-thrombotic activity [6]. The MPV was associated with the presence of diabetes [7] independently and elevated MPV is significantly associated with higher HbA1c levels and vice versa [8], but the PDW, platelet-large cell ratio (P-LCR), and thrombocytocrit (PCT) has not been reported or was based on small sample sizes.

If we could find the relationship between platelet indices and HbA1c, it could be applied to assess the risk of developing cardiovascular events and to execute early intervention and preventive measures rather than the time- and cost-consuming HbA1c levels.

Hence, the purpose of this study was to explore the relationship between platelet indicators (MPV, PDW, platelet count, P-LCR, PCT) and HbA1c.

MATERIALS AND METHODS

Subjects

This is a retrospective study performed in the Department of Clinical Laboratory Medicine of the First Affiliated Hospital of Shaoyang University from May 2017 to February 2018. The demographic characteristics of all individuals (886 males and 843 females) were drawn from the laboratory information system and the fasting plasma glucose (FPG), HbA1c, and complete blood counts were indispensable for all subjects. Patients were excluded if they fit one of the following criteria: subjects with platelet counts less than 100 x 10^9/L or more than 500 x 10^9/L to exclude subjects with possible hematological diseases which could affect platelet size, anemia, blood/platelet transfusion, pregnancy, lactation, acute or chronic infection, or blood disease. This study was approved by the Ethics Committee of the First Affiliated Hospital of Shaoyang University.

Laboratory analysis

Venous blood sample was drawn from the cubital vein after an overnight fast. The complete blood count of patients was measured using a Sysmex XN-1000 automatic hematology analyzer (Sysmex Corporation, Kobe, Japan). FPG was measured enzymatically on a Mindray BS800m autoanalyzer using the hexokinase method. HbA1c levels were measured by high performance liquid chromatography analyzer (HLC-723 G8, Tosoh, Tokyo, Japan). Standardization, calibration of instrument, and processing of samples were done according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were conducted with SPSS software (SPSS 20.0, IBM, USA). Data were presented as mean ± standard deviation (SD) for normal distribution variables (Kolmogorov-Smirnov test) and median (quartile range) for non-normal distribution variables. Continuous variables were compared using Student's *t*-test or the Mann-Whitney *U*-test as appropriate. p-values less than 0.05 were deemed as statistically significant.

RESULTS

The demographic characteristics of 1,729 subjects included in the analyses are presented in Table 1. The mean age was 63.3 (SD: 13.8) years and 886 (51.2%) were male. The mean FPG level was 7.74 ± 3.29 mmol/L and the mean HbA1c level was 7.27 ± 1.93%. It was obvious that the study population included a considerable number of individuals.

A positive and statistically significant correlation was noted between HbA1c and PDW, MPV, and P-LCR in the entire study cohort (Spearman's rho = 0.176, 0.138 and 0.149, p = 0.000, 0.000 and 0.00, respectively). While the correlation between HbA1c and PCT was poor (Spearman's rho = 0.041, p = 0.089) (Figure 1). We divided all the subjects into two subgroups according to the upper limit of the reference interval of each index. In Figure 2, the PDW, MPV, P-LCR, and glucose levels of T2DM patients in the higher HbA1c subgroups (≥ 6.5%) were significantly higher than that in lower HbA1c subgroups (< 6.5%) (Z-score or *t*-test = -6.286, -5.250, 5.603 and -22.667, all p < 0.01, respectively), but not the platelet and PCT (Z-score = -1.078 and -0.693, p= 0.281 and 0.488).

The platelets, MPV, P-LCR, PCT, HbA1c, and glucose levels were significantly higher in the higher PDW subgroup (≥ 17 fL) than that in the lower subgroups (< 17 fL) as shown in Figure 3 (Z-score/*t*-test = -14.320, -5.909, -22.719, 33.713, -7.509, and -3.914, all p < 0.01, respectively).

In the higher MPV subgroup (≥ 12 fL), the platelet, PDW, P-LCR, PCT, HbA1c, and glucose levels were significantly higher than that in the lower MPV subgroup (< 12fL) (Z-score or *t*-test = -16.807, -29.561, 47.383, -8.125, -5.077, and -3.122, all p < 0.01, respectively) (Figure 4).

The platelets, MPV, PDW, PCT, HbA1c, and glucose levels were significantly higher in the higher P-LCR subgroup (≥ 45%) than that in lower subgroup (< 45%)

Table 1. Characteristic of all subjects (n = 1,729).

Characteristics	
Age, mean ± SD, years	**63.3 ± 13.8**
Male/female, n/n (%/%)	**886/843 (51.2/8.8)**
FPG, mean ± SD, mmol/L	**7.74 ± 3.29**
Platelet, mean ± SD, x 10^9/L	**208.7 ± 64.1**
HbA1c, mean ± SD, %	**7.27 ± 1.93**
MPV, mean ± SD, fL	**11.24 ± 1.09**
PDW, mean ± SD, fL	**13.91 ± 2.64**
P-LCR, mean ± SD, fL	**34.91 ± 8.61**
PCT, mean ± SD, %	**0.231 ± 0.062**

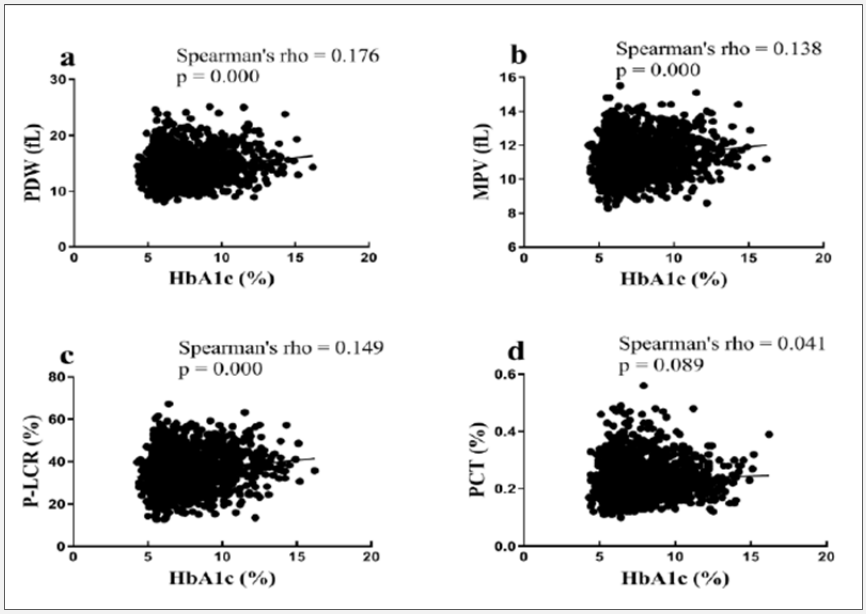

Figure 1. Correlation between HbA1c and PDW, MPV, P-LCR and PCT. PDW, MPV and P-LCR were positively related with HbA1c levels.

(Z-score = -14.395, -22.872, -23.498, -7.243, -4.912, and -2.885, all $p < 0.01$, respectively) (Figure 5).

The platelets, MPV, PDW, and P-LCR levels were significantly higher in the higher PCT subgroup (≥ 0.282 %) than that in the lower subgroup (< 0.282%) (Z-score or *t*-test = -26.184, -6.988, -7.273, and -7.450, all $p < 0.01$, respectively), but not the HbA1c and glucose levels (Z-score = -0.714 and -0.224, p = 0.475 and 0.823) (Figure 6).

DISCUSSION

Diabetes mellitus is a disease with a group of metabolic disorders sharing the common underlying feature of hyperglycemia. Platelet hyperactivity has been reported and supported by numerous studies in diabetic patients [5,9,10]. This study demonstrated that HbA1c and the values of PDW, MPV, and P-LCR were significantly and positively related in T2DM patients.

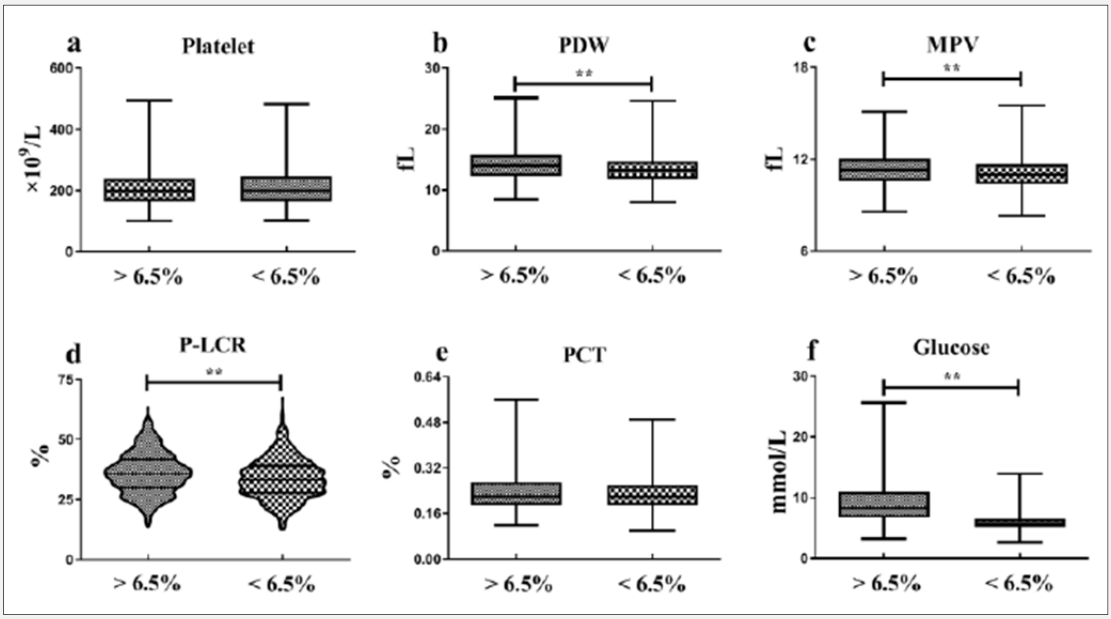

Figure 2. Platelet indices and glucose in different HbA1c subgroups. PDW, MPV, P-LCR, and glucose in the higher HbA1c subgroup were significantly higher than in the lower subgroup, ** p < 0.01.

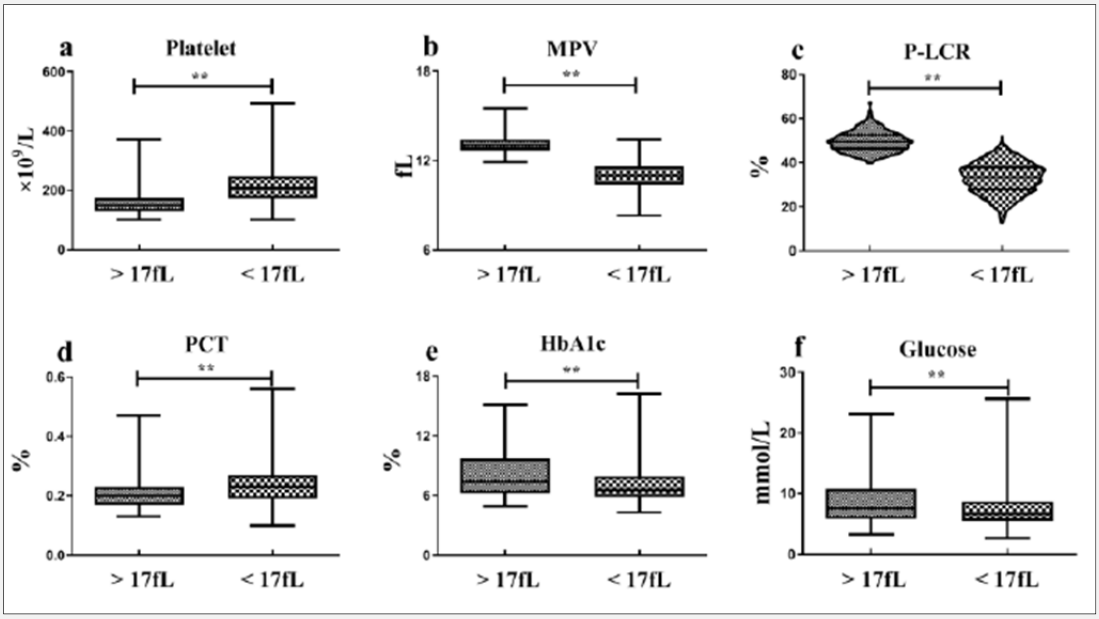

Figure 3. Platelet indices, HbA1c, and glucose in different PDW subgroups. Platelet counts and PCT were significantly lower and MPV, P-LCR, HbA1c, and glucose were significantly higher in the higher PDW subgroup than in the lower subgroup, ** p < 0.01.

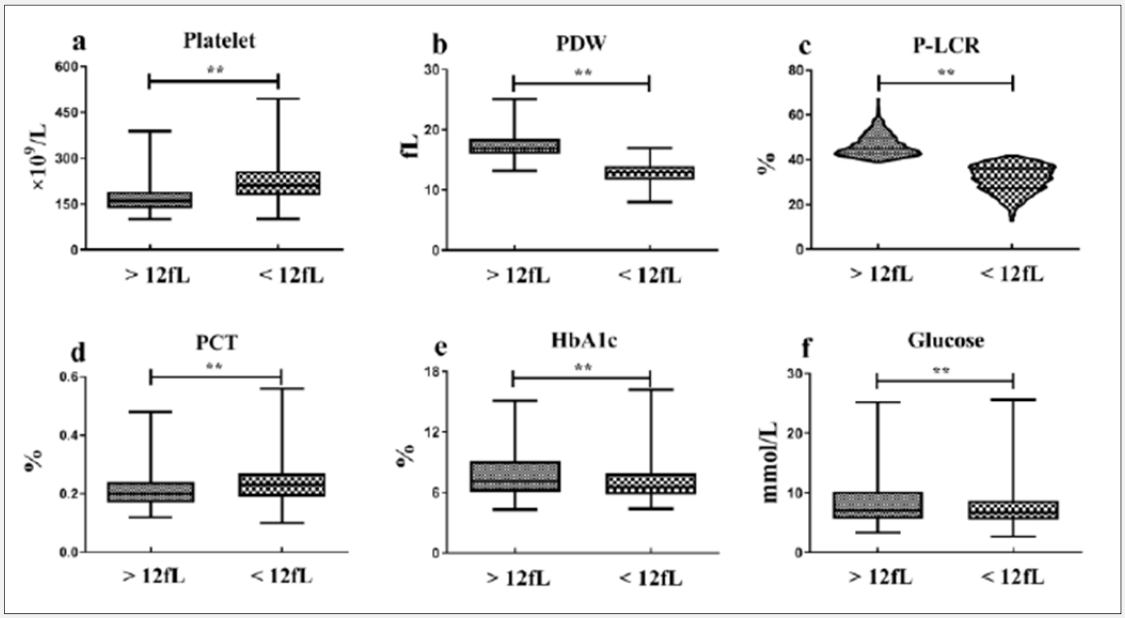

Figure 4. Platelet indices, HbA1c, and glucose in different MPV subgroups. Platelet counts and PCT were significantly lower and PDW, P-LCR, HbA1c, and glucose were significantly higher in the higher MPV subgroup than in the lower subgroup, ** p < 0.01.

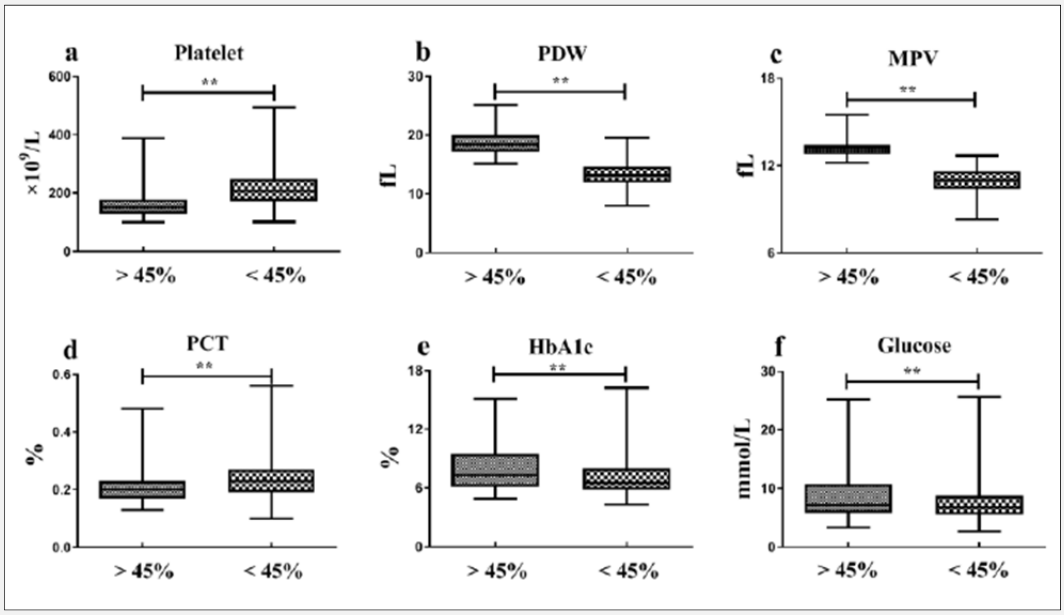

Figure 5. Platelet indices, HbA1c and glucose in different P-LCR subgroups. Platelet counts and PCT were significantly lower and PDW, MPV, HbA1c, and glucose were significantly higher in the higher P-LCR subgroup than in the lower subgroup, ** p < 0.01.

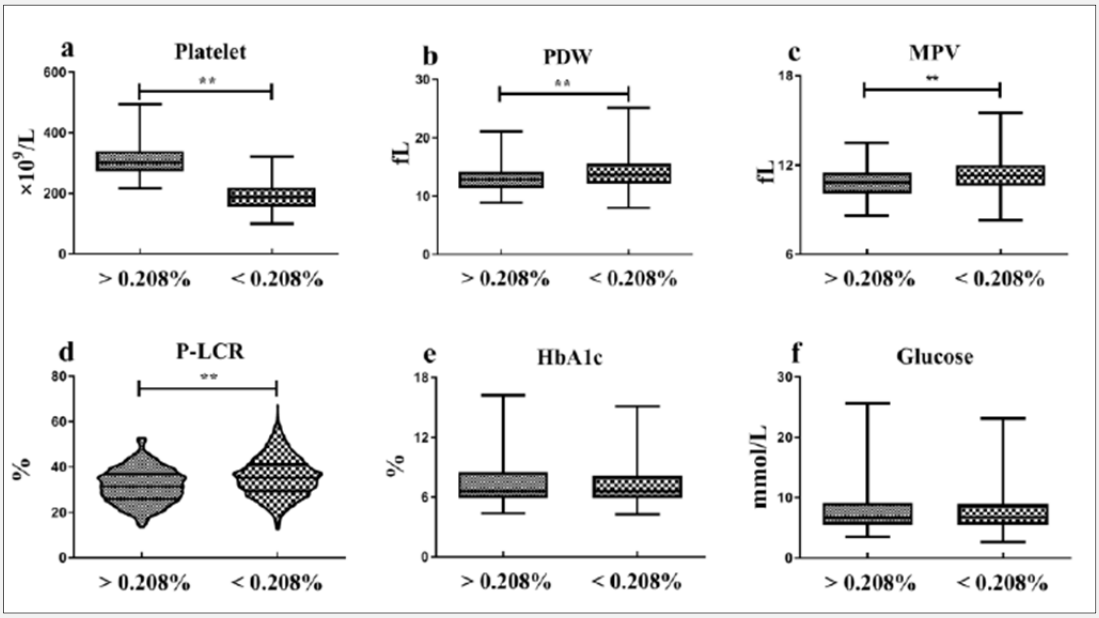

Figure 6. Platelet indices, HbA1c, and glucose in different PCT subgroups. Platelet counts was significantly higher and PDW, MPV, and P-LCR were significantly lower in the higher PCT subgroup than in the lower subgroup, ** $p < 0.01$.

Platelets from T2DM patients showed elevated reactivity and baseline activation and these characteristics are likely to give rise to the development and maintenance of the status of vascular complications [11]. Peripheral platelets are anucleate discoid cells that circulate in the bloodstream with a key role in hemostasis [12]. In the diabetic patients, the osmotic swelling due to raised blood glucose and a shorter lifespan of platelets might be one of the mechanisms to explain the increased MPV in DM [13].

In this study, we found that the MPV levels were closely related with the glucose control of T2MD patients as shown in the HbA1c level. Particularly, in the higher MPV subgroup, the PDW was higher simultaneously and vice versa, which means that the volume of all platelets was not swollen as a whole, but partly. Elevated MPV values in DM patients manifests larger platelet volume, which means stimulated thrombopoiesis and augmented platelet activation.

The P-LCR is a relatively new platelet volume parameter that often has not been quoted in literature. It is generated by only a few machines, with the Sysmex analyzer being one of them. P-LCR is the measure of larger platelets. As Jindal et al. [14] reported, P-LCR was significantly higher in diabetic patients compared to the control subjects. Besides, in this study, P-LCR was correlated with HbA1c level, and the higher HbA1c subgroup showed significantly higher P-LCR levels and vice versa.

CONCLUSION

In our study, MPV, PDW and P-LCR were significantly higher in diabetics with HbA1c levels ≥ 6.5% than in diabetics with HbA1c levels < 6.5%. This is in agreement with the studies conducted by Shilpi et al. [12]. Although the measurement of HbA1c has been considered as the most useful indicator of glucose control, its internal imperfection prompt us to look forward to new bio-markers. The ready availability of these parameters at no additional cost may encourage their utilization in clinical practice.

This study has some limitations. Firstly, this is a retrospective study. Secondly, patients were not categorized according to diabetic complications. Thirdly, platelet function tests could not be conducted on the sample to substantiate our findings further.

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Declaration of Interest:
The authors declared that there is no conflict of interest in this work.

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