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**Hyperglycemia metrics from continuous glucose monitoring are independently associated with platelet morphology in adults with type 1 diabetes**

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**Abstract**

**Introduction:** Platelet morphology indices are indirectly related to platelet reactivity and may link glycemic exposure to cardiovascular risk.

**Objectives:** We aimed to investigate associations between continuous glucose monitoring (CGM)-derived metrics and platelet morphology in adults with T1DM.

**Patients and methods:** In this cross-sectional study, we enrolled adults with T1DM without established cardiovascular disease. Platelet morphology indices were measured from fasting blood samples using the Sysmex XN-1000 analyzer within 2 hours of blood collection. Glucose profiles were assessed using CGM over 7-, 14-, and 30-day windows and calculated with Glyculator 3.0. We used Spearman correlation and multivariable linear regression models

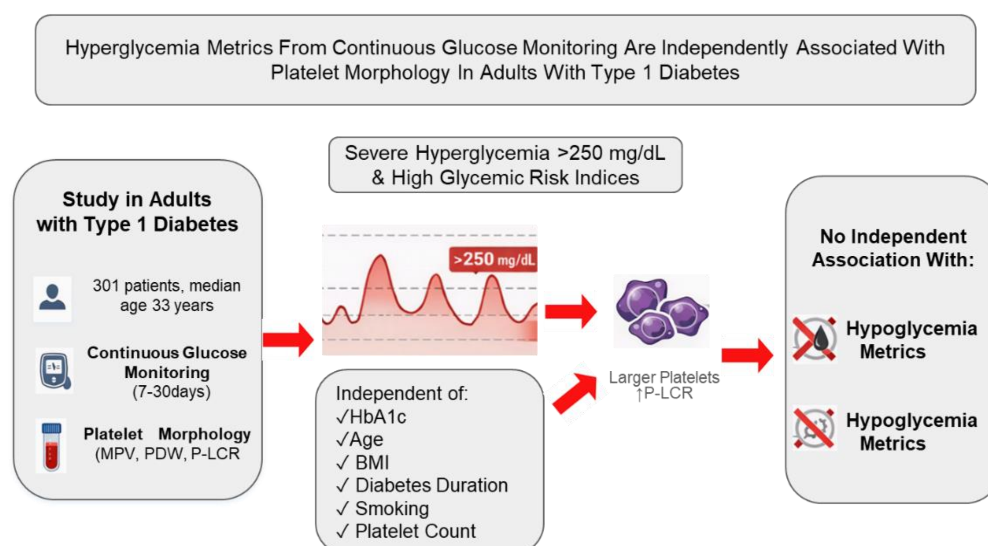
adjusted for age, sex, BMI, diabetes duration, C-reactive protein, glomerular filtration rate, HbA1c, smoking, and platelet count.

**Results:** We included 301 adults with T1DM [median age 33.1 (24.1-41.0), 44.5% men, diabetes duration 13 (7-19) years]. Platelet large cell ratio (P-LCR), mean platelet volume (MPV), and platelet distribution width (PDW)correlated positively with mean glucose (R = 0.27-0.30), time above range (TAR) level 2 ($P$ = 0.25-0.29), glycemic risk index (R = 0.28-0.30), and mean amplitude of glucose excursion (MAGE) (R = 0.20-0.22), and inversely with time in range (R = −0.25 to −0.30; all $P < 0.001$), but not with hypoglycemia indices. In multivariable models, hyperglycemia-related metrics remained independently associated with P-LCR (standardized $\beta$ 1.37-1.59; $\Delta R^2$ 0.014-0.024; $P = 0.002$); MAGE lost significance in the multivariable model after accounting for TAR level 2.

**Conclusion:** In adults with T1DM, platelet morphology independently relates to cumulative hyperglycemic exposure rather than glycemic variability or hypoglycemia.

**Key words**

blood glucose self-monitoring, blood platelets, diabetes mellitus type 1, hyperglycemi, platelet morphology




**Graphical abstract**

## Introduction

Type 1 diabetes mellitus (T1DM) represents an autoimmune metabolic disease that leads to the destruction of pancreatic β-cells and insulin deficiency [1]. Despite advances in glycemic monitoring, individuals with T1DM remain at increased risk of cardiovascular complications, which are the leading cause of morbidity and mortality in this population [2].

Platelets regulate not only hemostasis and thrombosis but also vascular inflammation and endothelial dysfunction [3,4]. Elevated mean platelet volume (MPV) and platelet distribution width (PDW) are associated with increased platelet activation [5]. MPV is a potential cardiovascular risk marker. People with an increased MPV are at higher risk of death due to ischemic heart disease, mortality following myocardial infarction, and restenosis following coronary angioplasty [5,6].

Platelet large cell ratio (P-LCR) quantifies the proportion of circulating platelets larger than 12 fL. MPV and PDW capture shifts toward larger platelet subpopulations [7]. Larger, hyperreactive platelets contain higher concentrations of dense granules and release greater amounts of prothrombotic and proinflammatory mediators, thereby contributing to diabetes-related vascular complications such as arterial stiffness and accelerated atherosclerosis [8,9].

Previous studies have demonstrated that individuals with type 2 diabetes (T2DM) exhibit significantly higher MPV, PDW, and P-LCR than the general population, indirectly reflecting enhanced platelet activation and aggregation. These abnormalities intensify further in the presence of microvascular complications [10,11,12].

In people with T2DM, MPV is strongly associated with fasting blood glucose, postprandial glucose, and HbA1C [13,14]. PDW also correlates positively with HbA1c [15]. Moreover, improvement of HbA1c led to a significant decrease in MPV [16].

In contrast, evidence in T1DM remains limited. Available data indicate that children with T1DM exhibit significantly higher MPV and PDW values compared to healthy controls

[16,17]. Children with diabetic ketoacidosis present increased MPV and PDW, which decrease following treatment [17]. To date, no studies have examined the relationship between platelet morphology and CGM–derived metrics in adults with T1DM.

This study aimed to assess platelet morphology indices (MPV, PDW, and P-LCR) and their associations with CGM-derived glycemic metrics in adults with T1DM.

## Patients and methods

**Data collection** Between February 2024 and December 2025, we recruited adults with T1DM under the care of our Diabetology Department. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki [18] and was approved by the Ethical Committee of Poznan University of Medical Sciences (approval No.848/23). All participants gave their written informed consent to participate in the study. Eligibility criteria included age between 18 and 50 years (to avoid confounding from age-related comorbidities and physiological changes that could affect study outcomes), a confirmed diagnosis of T1DM based on diabetes-associated autoantibodies, and a minimum diabetes duration of one year. Individuals were excluded if they had severe infection, clinically active inflammatory or systemic disease at the time of assessment, cardiovascular disease (defined based on medical history of clinically overt macrovascular disease, including prior myocardial infarction, stroke, coronary artery disease, peripheral arterial disease, or previous coronary or peripheral revascularization), used antiplatelet agents (e.g., aspirin) or NSAIDs during the last 14 days, or if they used their CGM system less than 70 % of the analyzed time.

**Basic assessment** A questionnaire was administered to document medical history, diabetes-related complications, and comorbidities. To screen for diabetic kidney disease, urine was collected for albumin-creatinine ratio (ACR), and blood was drawn for serum creatinine measurement. Fundoscopy was conducted by an experienced ophthalmologist following

pharmacologic pupil dilation to evaluate diabetic eye disease. Diabetic peripheral neuropathy was assessed using standard bedside tests for tactile, vibration, and temperature sensation.

**Laboratory analysis** All blood samples were collected in the morning between 7:00 and 8:00 a.m. after an overnight fast of 8–12 hours. Venous blood was drawn into standardized tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA). Measurements of P-LCR, MPV, PDW, and other hematological parameters were performed within 120 minutes of sample collection, after which samples were maintained at room temperature (18–25 °C). Complete blood counts were analyzed using the Sysmex XN-1000 analyzer (Sysmex Corporation, Japan).

To reduce pre-analytical and analytical variability, all samples were collected, handled, and processed according to identical protocols. MPV was used as an indicator of mean platelet size, PDW was derived from the platelet volume histogram at 20% of the distribution peak, and P-LCR was defined as the percentage of circulating platelets with a volume exceeding 12 fL. Platelet index reference ranges were adopted according to the local laboratory standards: PDW, 10–17.4 fL; MPV, 7–12 fL; and P-LCR, 19.3%–47.1%. The same analyzer was used to assess red and white blood cell morphology.

Biochemical parameters, including lipid profile, transaminases, creatinine, C-reactive protein, thyroid-stimulating hormone, and HbA1c, were measured using a Cobas Pure analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). Low-density lipoprotein cholesterol was calculated using the Friedewald formula, except when triglyceride concentrations exceeded 400 mg/dL, in which case LDL cholesterol was measured directly [19].

**Glycemia analysis** The devices used for CGM included Dexcom G7 or One+ (Dexcom, San Diego, USA), and FreeStyle Libre 2 (Abbott Diabetes Care, Alameda, USA). CGM data were collected for all participants and analyzed using Glyculator 3.0 software - a web-based tool to calculate glycemic variability metrics indices from different CGMs [20].

Data were evaluated over a 7-day, 14-day, and 30-day window, counting backward from the laboratory test, to reflect glycemic exposure relevant to platelet production (4–7 days) and platelet lifespan (7–10 days) [21,22]. These windows also capture stable CGM metrics, as two weeks of CGM data reliably reflect longer-term glycemic patterns [23,24]. We analyzed glucose profiles across three time intervals: 24-hour (total), daytime (06:00 a.m. to midnight), and overnight (midnight to 06:00 a.m.).

The most clinically recognized measure is TIR, defined as the percentage of time glucose levels remain within the target range of 70–180 mg/dL. International guidelines from the ADA and EASD recommend maintaining a TIR above 70% as an indicator of adequate metabolic control [23].

Other key CGM-derived metrics include:

- Mean glucose - the average glucose level over the monitoring period.
- Standard deviation (SD): the degree of absolute variability around the mean glucose.
- Coefficient of variation (CV): the relative variability (SD divided by mean, expressed as a percentage); values above 36% suggest unstable glycemic control.
- Time below range (TBR): time spent in hypoglycemia, further categorized into level 1 (55–70 mg/dL) and level 2 (<55 mg/dL).
- Time above range (TAR): time spent in hyperglycemia, including level 1 (180–250 mg/dL) and level 2 (>250 mg/dL) [25].
- Time in tight range (TITR): the percentage of time within a stricter range of 70–140 mg/dL, reflecting tighter glycemic control [26].
- M100: reflects the average deviation of glucose from the ideal value of 100 mg/dL; lower values indicate greater stability, while higher values signal greater variability [27].

- J-index: integrates both mean glucose and SD, calculated as 0.001 × (mean + SD)$^2$; higher values suggest poorer overall control [28].
- GRADE (Glycemic Risk Assessment Diabetes Equation): assesses glycemic risk by assigning penalties for both hypo- and hyperglycemia
- GRADE-eugly, GRADE-hyper, GRADE-hypo: subcomponents that reflect time spent in each respective glycemic range [29].
- LBGI (Low Blood Glucose Index) and HBGI (High Blood Glucose Index): risk scores for hypo- and hyperglycemia, respectively, with higher scores indicating greater risk of clinically significant excursions [30].
- MAGE (Mean Amplitude of Glycemic Excursions) and MODD (Mean of Daily Differences): traditional measures of intraday and interday variability, respectively [27].
- ADRR (Average Daily Risk Range): an overall estimate of daily glycemic risk, incorporating both LBGI and HBGI [31].
- GRI (Glycemic Risk Index): a newer metric that condenses glucose distribution into a single risk-weighted score, validated against clinical outcomes [32].

**Statistical analysis** We performed our analyses in R (version 4.3.3). Categorical variables were reported as counts with percentages. Data distribution was assessed using visual inspection of histograms and the Shapiro–Wilk test. Continuous variables were presented as median (interquartile range) or mean ± standard deviation, as appropriate.

Sample size was determined a priori to ensure adequate power to detect associations between CGM-derived glycemic metrics and platelet morphology indices. Based on an assumed correlation coefficient of $r = 0.20$, with 80% power and a two-sided $\alpha$ of 0.01, the required sample size was 288 participants.

The adequacy of the sample size for multivariable linear regression was assessed using established recommendations for regression models. The models included 9 prespecified

clinical covariates in the base model and one CGM-derived metric added individually, resulting in 10 predictors. With 301 participants in the final analytical cohort, the study provided approximately 30 participants per predictor, exceeding commonly used recommendations for multiple linear regression, including Green's criteria of $N \geq 50 + 8m$ for testing the overall model and $N \geq 104 + m$ for testing individual predictors.

To account for potential missing data, the target sample size was increased by 15%, resulting in a planned recruitment of approximately 340 participants.

Associations between platelet indices and CGM–derived metrics were evaluated using Spearman's rank correlation coefficients (R). To account for multiple testing, false discovery rate (FDR) correction was applied using the Benjamini–Hochberg procedure, separately for each platelet index.

Between-group comparisons of qualitative variables were performed using Pearson's chi-square test or Fisher's exact test, as appropriate, depending on expected cell counts.

Differences in correlation strength were evaluated using Steiger's Z test for dependent correlations sharing a common variable**.**

Participants were stratified into tertiles according to selected CGM-derived metrics. Differences in P-LCR across tertiles were assessed using the Kruskal–Wallis test. When the overall test was statistically significant, post hoc pairwise comparisons were performed using Dunn's test with Holm adjustment for multiple comparisons.

Multivariable linear regression models were constructed with P-LCR as the dependent variable. Covariates were selected a priori based on clinical relevance and previous literature and included age, sex, body mass index, diabetes duration, C-reactive protein, estimated glomerular filtration rate, HbA1c, smoking status, and platelet count in a common base model. Each CGM-derived metric was subsequently added individually to the base model. Standardized $\beta$ coefficients reflect the change in P-LCR per 1 SD increase in the predictor.

Assumptions of multivariable linear regression were assessed using standard diagnostic procedures. Residual normality was evaluated using the Shapiro–Wilk test and visual inspection of Q-Q plots. Homoscedasticity was assessed using residual-versus-fitted plots and the Breusch–Pagan test. Influential observations were evaluated using Cook's distance, leverage values, and standardized residuals. Multicollinearity was assessed using variance inflation factors (VIFs). To reduce collinearity among CGM-derived metrics, each CGM-derived metric was added separately to the same prespecified covariate model. In case of heteroscedasticity, sensitivity analyses using heteroskedasticity-consistent HC3 robust standard errors were performed.

To isolate glycemic variability independent of severe hyperglycemic exposure, residualized variability metrics were generated for CV and MAGE. The residuals ($\varepsilon_i$) from these models were extracted and used as residualized variability measures, representing the component of glycemic variability not explained by exposure to severe hyperglycemia.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant unless otherwise specified. For correlation analyses involving multiple comparisons, FDR correction was applied using the Benjamini–Hochberg procedure.

## Results

**General characteristics** We recruited 375 participants with T1DM but 45 were excluded due to abnormal laboratory results (elevated CRP, platelet count outside the reference range), and 25 due to incomplete CGM data. Finally, we included 301 adults with T1DM (Table 1). Participants had a median age of 33.1 years (24.1–41.0), and 44.5% were men. The median diabetes duration reached 13 years (7–19), and the median HbA1c was 7.6% (6.8–8.4). Most participants used the FreeStyle Libre 2 system (n=271), whereas the remaining individuals used Dexcom (n=30). Over 7 days, participants had a median mean glucose of 167.2 mg/dL (143.9–

195.5) (Supplementary Table S1). Nearly one-third of participants met the target for time in range, while 34.2% had time above range level 2 ≥5%. Platelet morphology parameters were mostly within reference ranges (n= 232; 77.1%). A total of 58 participants (19.3%) had at least one elevated platelet index, whereas 11 (3.7%) had at least one decreased platelet index.

Median platelet large cell ratio (P-LCR) was 26.2% (21.5–31.7). A small subset of participants had chronic inflammatory or immune-mediated conditions in stable form, including celiac disease (n = 7), psoriasis or psoriatic arthritis (n = 2), multiple sclerosis (n = 1), microscopic colitis (n = 1), and autoimmune pancreatitis (n = 1).

**Associations of platelet indices** We observed consistent correlations between platelet indices (P-LCR, MPV, and PDW) and CGM metrics (Table 2). All three platelet indices correlated positively with markers of hyperglycemia, including mean glucose, TAR level 2, GRI, and hyperglycemia-related risk indices with comparable effect sizes (R= 0.25–0.30, all $P < 0.001$ after FDR correction). In contrast, platelet indices correlated inversely with time in range (TIR) and time in tight range (TITR) (R = −0.25 to −0.30, $P < 0.001$).

Measures of glycemic variability showed weaker and less consistent associations. MAGE correlated modestly with P-LCR, MPV, and PDW (R = 0.20–0.22, $P < 0.001$), whereas CV demonstrated only weak correlations, which did not consistently remain significant after FDR correction. Hypoglycemia-related metrics (TBR, LBGI) showed no significant associations with any platelet index.

Among clinical and laboratory variables, all platelet indices correlated inversely with platelet count (R = −0.38, $P < 0.001$) and positively with HbA1c and mean corpuscular volume (Table 3). None of the platelet indices showed significant correlations with age, diabetes duration, body mass index, blood pressure, lipid profile, renal function, or inflammatory markers. The most important associations are summarised in Figure 1.

Participants with TIR ≥70% differed in the distribution of platelet index categories compared with those with lower TIR ($\chi^2 = 7.50$, df = 2, P = 0.02), with a lower prevalence of elevated values (1.3% vs 4.4%) and a higher prevalence of decreased values (29.3% vs 15.9%), while the proportion within the reference range was comparable(69.3% vs 79.7%).

**Platelet–glycemic associations across circadian periods and time of the analysis window**

Daytime and nighttime analyses revealed similar patterns (Table 1). The strength of correlations between platelet indices (P-LCR, MPV, and PDW) and CGM metrics did not differ across 24-hour, daytime, and nighttime periods - Steiger's test showed no differences across any platelet index (all $P > 0.15$).

The strength of correlations between platelet indices (P-LCR, MPV, and PDW) and hyperglycemia-related CGM metrics did not differ across 7-, 14-, and 30-day analysis windows based on Steiger's test results (all $P > 0.36$), indicating temporal robustness of the observed associations (Supplementary Tables S2,S3).

**Collinearity of PDW, MPV, and P-LCR** All 3 platelet indices were highly related to each other. The strength of correlations between hyperglycemia-related CGM metrics and platelet indices did not differ significantly between P-LCR, MPV, and PDW. Steiger's test showed no differences for mean glucose, TAR level 2, or GRI (all $P > 0.26$), indicating comparable sensitivity of platelet volume indices to hyperglycemic exposure. Therefore, we chose P-LCR for further analysis because it most directly reflects the large, active platelets.

**Tertile analyses of CGM metrics** For TAR level 2 (%), P-LCR differed significantly across tertiles (Kruskal–Wallis $\chi^2 = 21.72$, $p < 0.001$). Median P-LCR increased from T1 to T3 [T1: 23.5% (19.3–29.0), T2: 25.6% (21.4–29.2), T3: 28.3% (23.1–34.2)]. In post hoc analysis, P-LCR was significantly higher in T3 than in both T1 (adjusted $p < 0.001$) and T2 (adjusted $p = 0.004$), whereas T1 and T2 did not differ significantly.

For GRI, P-LCR also differed significantly across tertiles (Kruskal–Wallis $\chi^2 = 19.21$, $p < 0.001$). Median P-LCR was 23.4% (18.9–28.4) in T1, 26.4% (22.2–31.3) in T2, and 27.6% (22.9–34.1) in T3. Dunn's post hoc test showed significantly higher P-LCR in T2 compared with T1 (adjusted $p = 0.009$) and in T3 compared with T1 (adjusted $p < 0.001$), while T2 and T3 did not differ significantly.

For mean glucose, there was a significant difference in P-LCR across tertiles (Kruskal–Wallis $\chi^2 = 25.36$, $p < 0.001$). Median P-LCR increased from 22.9% (19.3–27.9) in T1 to 26.5% (22.4–30.9) in T2 and 27.8% (23.0–34.4) in T3. Post hoc comparisons confirmed significantly higher P-LCR in T2 than in T1 (adjusted $p = 0.004$) and in T3 than in T1 (adjusted $p < 0.001$). The difference between T2 and T3 did not reach statistical significance (adjusted $p = 0.06$).

For TIR (%), the association was inverse. P-LCR differed significantly across tertiles (Kruskal–Wallis $\chi^2 = 22.37$, $p < 0.001$), with median values of 27.6% (23.0–34.1) in T1, 26.6% (22.4–31.5) in T2, and 22.9% (18.9–28.3) in T3. In post hoc analysis, P-LCR was significantly lower in T3 than in both T1 (adjusted $p < 0.001$) and T2 (adjusted $p = 0.002$), whereas T1 and T2 did not differ significantly.

For MAGE, P-LCR differed significantly across tertiles, although the separation between groups was less pronounced than for hyperglycemia-related metrics (Kruskal–Wallis $\chi^2 = 12.19$, $p = 0.002$). Median P-LCR was 23.8% (19.6–29.3) in T1, 26.8% (21.8–30.7) in T2, and 27.3% (22.8–34.1) in T3. Dunn's post hoc test showed a significant difference only between T1 and T3 (adjusted $p = 0.002$), while adjacent tertiles did not differ significantly.

For CV, P-LCR also differed across tertiles, but the effect was weaker (Kruskal–Wallis $\chi^2 = 8.03$, $p = 0.02$). Median P-LCR was 24.6% (19.1–30.3) in T1, 26.5% (21.4–30.5) in T2, and 27.1% (22.6–33.5) in T3. In post hoc analysis, only the difference between T1 and T3 was statistically significant (adjusted $p = 0.01$), whereas T1 vs T2 and T2 vs T3 were not significant.

**Linear regression analyses** In multivariable linear regression analyses adjusted for age, sex, body mass index, diabetes duration, C-reactive protein, estimated glomerular filtration rate, HbA1c, smoking status, and platelet count, several CGM-derived metrics showed independent associations with platelet large cell ratio (P-LCR) (Supplementary Table S4).

Across models, platelet count was consistently and inversely associated with P-LCR, and male sex showed a stable positive association, whereas diabetes duration reached statistical significance only in a limited number of models.

Hyperglycemia-related metrics demonstrated the most consistent and robust associations. TAR level 2, glucose risk index (GRI), and mean glucose were all independently and positively associated with P-LCR, with standardized β coefficients ranging from 1.37 to 1.59 and statistically significant increases in explained variance ($\Delta R^2$ 0.014–0.024). Similarly, indices reflecting overall glycemic exposure and risk, including ADRR, HBGI, J-Index, and GRADE, were associated with higher P-LCR, each contributing additional explanatory power beyond the base model ($\Delta R^2$ up to 0.027)

Measures of glycemic distribution showed concordant results. Higher glucose, absolute glucose range, and TAR (%) were positively associated with P-LCR, whereas time in range (TIR) and time in tight range (TITR) were inversely associated. In contrast, lower-range metrics, including Q1 glucose and hypoglycemia-weighted indices, did not show significant associations.

Glycemic variability metrics exhibited weaker and less consistent effects. Although SD, MAGE, CV, and SD of daily CV were each independently associated with P-LCR when entered separately into the model, their effect sizes were smaller, and their contributions to explained variance were modest ($\Delta R^2 \leq 0.016$).

Across all models, the inclusion of CGM-derived metrics improved model fit compared with the base model alone, with final $R^2$ values ranging from 0.311 to 0.329. The strongest

incremental gains in explained variance were observed for ADRR, SD, GRI, and TAR level 2. These results are visually summarized in Figure 3.

Diagnostic assessment of the main multivariable linear regression models showed no major violations of residual normality or multicollinearity. Residual normality was acceptable across all principal models (all Shapiro–Wilk $p > 0.05$), and VIF values were low (maximum VIF range: 1.24–2.40), indicating no substantial multicollinearity. The Breusch–Pagan test suggested heteroscedasticity in several models; therefore, sensitivity analyses using heteroskedasticity-consistent HC3 robust standard errors were performed. The main associations between CGM-derived hyperglycemia metrics and P-LCR remained statistically significant after HC3 correction (Supplementary Table S5).

**Hyperglycemia versus glycemic variability** In models including either CV or MAGE, the TAR level 2 remained a significant positive predictor of P-LCR, while CV and MAGE showed no independent association.

These findings were unchanged when CV and MAGE were replaced by their residual values, representing variability components independent of severe hyperglycemia. Platelet morphology related to exposure to severe hyperglycemia rather than glucose variability per se (Supplementary Figure S1).

## Discussion

**Hyperglycemia as the primary correlate of platelet morphology** This study demon-nstrates that in adults with T1DM, platelet morphology indices are primarily associated with exposure to hyperglycemia rather than with glycemic variability. CGM-derived metrics reflecting chronic and severe hyperglycemia, particularly TAR level 2, HBGI, and composite hyperglycemic risk indices, showed consistent and robust associations with MPV, PDW, and P-LCR. These associations remained significant after adjustment for HbA1c and other factors,

suggesting that CGM captures clinically relevant aspects of glycemic exposure that are not fully reflected by HbA1c alone. To the best of our knowledge, this is the first study to demonstrate such associations in adults with T1DM.

Our study is consistent with data from T2DM that confirmed the positive association between HbA1c and MPV [13,14,15]. Our results are only partly consistent with the findings of Özdemir et al., who reported no significant associations between glucose variability indices (SD, CV, MODD) and mean platelet volume in patients with T2DM, despite a detailed SMBG-based assessment of intraday and day-to-day variability [33]. In our group, glycemic variability showed no independent relevance for platelet morphology. However, in contrast to that study, we demonstrate that CGM-derived metrics of hyperglycemic exposure, particularly severe hyperglycemia, are independently associated with platelet morphology.

**Limited role of glycemic variability and hypoglycemia** Although measures of glycemic variability showed modest associations with platelet morphology, their effects were substantially attenuated after accounting for severe hyperglycemia. Residualized variability metrics, independent of TAR level 2, were not associated with platelet indices, indicating that glucose variability per se is unlikely to be a major determinant of platelet size in T1DM.

Hypoglycemia indices were not associated with platelet morphology. This finding suggests that platelet activation may be driven predominantly by sustained hyperglycemic exposure rather than by short-term glucose oscillations or hypoglycemia events [14,34].

Tertile analyses supported differences in P-LCR across categories of hyperglycemic exposure, with the highest P-LCR generally observed among participants in the least favorable glycemic tertiles. In contrast, glycemic variability metrics showed weaker discrimination, with significant differences mainly between extreme tertiles.

**Similarity across circadian periods and CGM time windows** The associations between platelet morphology indices and hyperglycemia-related CGM metrics were consistent across

daytime and nighttime periods as well as across 7-, 14, and 30-day CGM analysis windows. This temporal stability supports the concept that platelet morphology reflects cumulative glycemic burden rather than transient metabolic fluctuations. Similarly, Shat et al. showed that daytime and nighttime CGM metrics have a similar influence on HbA1c in adults with T1DM [35]. Based on previous studies, different time windows of CGM analysis are highly correlated, and two weeks of CGM sampling with >70% CGM use is recommended to accurately reflect 90 days of glycemic metrics [23,24].

**CGM Metrics Outperform HbA1c** Multiple CGM-derived indices outperformed $HbA_{1c}$ in correlation with platelet indices. Although $HbA_{1c}$ has long served as the cornerstone for glycemic assessment, it does not capture time spent in hyperglycemia and outside the target range [36]. Moreover, $HbA_{1c}$ is dependent on other factors, including hemoglobin, and may be biased in the case of anemia. Our multivariable models showed that once CGM metrics were included, $HbA_{1c}$ lost its predictive value. This finding is consistent with the work of Battelino et al. and Vigersky & McMahon, who both advocate for TIR, TAR, and TBR as superior metrics for complication risk stratification [23,37]. In our cross-sectional study, TAR level 2, GRI, and ADRR emerged as the strongest single correlates of P-LCR, even after adjusting for $HbA_{1c}$.

Platelets have a lifespan of approximately 10 days [21]. Thrombopoiesis typically takes 5 days [22]. HbA1c, which reflects average glycemia over 2-3 months, may represent a time window too long to capture changes in current platelet morphology [38]. However, longitudinal studies are needed to determine the duration and intensity of hyperglycemic exposure required to influence platelet morphology.

**Association or mechanistic?** Although our study is the first to demonstrate an association between hyperglycemia and platelet morphology in adults with T1DM, the underlying mechanisms require further investigation. It remains unclear whether

hyperglycemia primarily alters thrombopoiesis, directly modifies the size of circulating platelets, or influences both processes.

Available evidence suggests that hyperglycemia influences platelet size and reactivity through partially overlapping but mechanistically distinct pathways. Platelet size, reflected by MPV, is largely determined during thrombopoiesis and depends on megakaryocyte maturation, ploidy, and platelet turnover rather than on secondary activation of circulating platelets [4,39]. Hyperglycemia may alter the bone marrow microenvironment and promote the release of larger platelets, which is consistent with observations linking increased platelet size to conditions associated with heightened platelet turnover. Hyperglycemia's effects on circulating platelets primarily disturb platelet function, including enhanced adhesion, aggregation, and prothrombotic signaling [40]. Although larger platelets tend to exhibit greater metabolic activity and higher prothrombotic potential, platelet size indices remain indirect markers of platelet reactivity and cannot substitute for functional platelet assays [39]. Therefore, the associations observed in the present study likely reflect hyperglycemia-related alterations in platelet production dynamics rather than acute functional activation of circulating platelets.

Chronic hyperglycemia in diabetes promotes oxidative stress, endothelial damage, and increased platelet adhesion. Hyperglycemia activates polymorphonuclear neutrophils, which induce reactive oxygen species, enhancing the inflammatory process [41,42]. Diabetic platelets overproduce prothrombotic mediators, such as thromboxane A2 and P-selectin. Simultaneously, they resist endogenous inhibitors, including nitric oxide and prostacyclin, resulting in a sustained proinflammatory and prothrombotic state [4,43].

Li et al. demonstrated that hyperglycemia-induced endothelial YAP activation aggravates platelet activation and arterial thrombus formation via PGE2/EP3 signaling [44]. Sagar et al. demonstrated that individuals with T1DM having advanced insulin resistance (eGDR $<6$ mg $kg^{-1}$ $min^{-1}$) showed significantly greater platelet activation and reduced

sensitivity to platelet inhibition compared to those with normal insulin sensitivity [45]. El-Hawy et al. identified genetic determinants of platelet morphology in T1DM children, showing that the rs7961894 CT genotype was a predictor of MPV, PDW, and PCT changes, with these indices correlating substantially with atherogenic lipid parameters [46].

Activated platelets release a broad range of proinflammatory cytokines and chemokines that amplify chronic low-grade inflammation and exacerbate endothelial dysfunction and vascular remodelling. These processes promote microthrombus formation and impair capillary perfusion [3].

**Limitations** This study has several limitations. First, the cross-sectional design prevents us from inferring causality. Second, we assessed platelet morphology without functional platelet assays, which could provide additional mechanistic insight. Third, although blood sampling and laboratory procedures were standardized, we cannot fully exclude pre-analytical influences on platelet indices, particularly those related to EDTA-induced platelet swelling and the time from sampling to analysis; although this interval was kept within 120 minutes, it was not recorded for each participant.

The a priori sample size calculation was based on Pearson's correlation coefficient, whereas Spearman's rank correlations were ultimately used due to non-normal data distributions. However, the observed effect sizes ($R = 0.25–0.30$) exceeded the assumed correlation of $r = 0.20$, which compensates for the marginally lower efficiency of the non-parametric test. Finally, despite comprehensive adjustment for clinically relevant covariates, residual confounding may still influence the observed associations. Although we excluded individuals with active chronic diseases and infections, a small number of participants had stable chronic inflammatory conditions, which may have influenced platelet indices.

**Strengths and practical implications** We analyzed a large, well-characterized cohort of adults with T1DM using standardized laboratory procedures and high-quality CGM data. The

comprehensive assessment of glycemia included multiple CGM-derived metrics capturing hyperglycemia, hypoglycemia, and glycemic variability across different circadian periods and time windows.

MPV, P-LCR, and PDW are routinely generated by automated hematology analysers at no additional cost, require no special preparation from patients, and exhibit high inter-laboratory reproducibility when processed within standardized pre-analytical protocols [8]. Their association with CGM-derived hyperglycemia metrics suggests that they may serve as integrative biomarkers linking metabolic control to thrombotic and inflammatory pathways. Our results underscore the clinical importance of minimizing time spent in severe hyperglycemia, in addition to achieving target HbA1c levels. Effective ketoacidosis treatment in children with T1DM was associated with decreased MPV values [17]. Improvement of HbA1c led to a significant decrease in MPV among people with T2DM, but further longitudinal studies in the T1DM population are needed to investigate if better glycemic control and avoiding severe hyperglycemia decreases platelet indices and platelet reactivity [16]. Another important question is whether platelet morphology and CGM-derived hyperglycemia metrics are associated with future microvascular complications and cardiovascular events in the T1DM population.

**Conclusions** In adults with T1DM, platelet morphology indices are closely and independently associated with CGM-derived measures of hyperglycemia, whereas glycemic variability shows limited independent relevance, and there is no association with hypoglycemia indices. Severe and sustained hyperglycemic exposure, rather than glucose fluctuations, seems to be the principal determinant of platelet enlargement; however, further prospective studies are needed to confirm this hypothesis. These findings support the clinical importance of minimizing exposure to severe hyperglycemia in individuals with T1DM.

## Article information

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**Contribution statement** MK conceived the study, analyzed and interpreted the data, and was a major contributor in writing the manuscript. DN contributed to study design, recruitment, and clinical interpretation. AK contributed to data collection, statistical analysis, and manuscript preparation. SM, AL, and PH participated in data acquisition and analysis of continuous glucose monitoring records. AGW assisted in data collection and literature review. AU and AA contributed to study conception, interpretation of findings, and critical revision of the manuscript. DZZ supervised the study, contributed to its conception and design, and critically revised the manuscript. All authors read and approved the final manuscript.

**AI statement** During the preparation of this work, the authors used Grammarly and ChatGPT to improve the clarity, readability, and language of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication

**Availability of data and materials** The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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**Table 1. Baseline characteristics of the study group**

| **Variable** | **Total cohort (N = 301)** |
|---|---|
| **General demographic data** | |
| Age, years | 33.1 [24.1 - 41.0] |
| Sex, men | 134(44.5%) |
| **Body composition and anthropometry** | |

| Height, m | 1.72 [1.66 - 1.81] |
| --- | --- |
| Weight, kg | 74 [63 - 87] |
| BMI, $kg/m^2$ | 24.96 [21.97 - 27.66] |
| Waist circumference, m | 0.86 [0.77 - 0.95] |
| Hip circumference, m | 1.02 [0.98 - 1.09] |
| WHR | 0.84 [0.77 - 0.9] |
| **Diabetes-related clinical characteristics** | |
| Diabetes duration, years | 13 [7 - 19] |
| DII, U/kg | 0.58 [0.46 - 0.74] |
| HbA1c, % | 7.6 [6.8 - 8.4] |
| Insulin pump, n | 72(23.9%) |
| Free Style Libre | 273(90.7%) |
| TIR > 70% | 92(30.6%) |
| TAR level 2 < 5% | 103(34.2%) |
| **Arterial pressure** | |
| SBP, mmHg | 124.13(12.45) |
| DBP, mmHg | 75.89(8.67) |
| **Hematological parameters** | |
| WBC, $\times 10^3/\mu L$ | 6.4 [5.51 - 7.28] |
| RBC, $\times 10^6/\mu L$ | 4.72 [4.46 - 5.07] |
| Hb, g/dL | 14.34(1.31) |
| Hct, % | 41.1 [38.9 - 44.2] |
| MCV, fL | 87.4 [84.9 - 90.1] |
| MCH, pg | 30.4 [29.4 - 31.4] |
| RDW-CV, % | 12.3 [11.8 - 12.8] |
| **Platelet morphology** | |

| PLT, $\times 10^3/\mu L$ | 252 [219 - 298] |
|---|---|
| MPV, fL | 10.2 [9.6 - 10.9] |
| PDW, fL | 11.5 [10.4 - 12.9] |
| P-LCR, % | 26.2 [21.5 - 31.7] |
| PCT, % | 0.26 [0.23 - 0.3] |
| **Lipid profile** | |
| Total cholesterol, mg/dL | 179 [159 - 208] |
| LDL cholesterol, mg/dL | 98 [75.5 - 120.5] |
| HDL cholesterol, mg/dL | 92 [66 - 124] |
| Non-HDL cholesterol, mg/dL | 72 [59 - 105] |
| Triglycerides, mg/dL | 83.3 [66.1 - 107] |
| **Other laboratory results** | |
| Sodium, mmol/L | 139 [138 - 140] |
| Potassium, mmol/L | 4.24 [4.03 - 4.53] |
| ALT, U/L | 16 [12 - 22] |
| AST, U/L | 20 [17 - 24] |
| Creatinine, mg/dL | 0.8 [0.71 - 0.91] |
| eGFR, mL/min/1.73 $m^2$ CKD-EPI 2021 | 110.69 [99.42 - 119.26] |
| ACR [mg/g] | 3 [2.08 - 5] |
| CRP, mg/L | 0.97 [0.6 - 1.95] |
| TSH, µIU/mL | 1.76 [1.15 - 2.59] |
| **Diabetic complications** | |
| At least one complication | 57(18.9%) |
| Diabetic peripheral neuropathy | 20(6.6%) |
| Non-proliferative diabetic retinopathy | 43(14.3%) |
| Proliferative diabetic retinopathy | 9(3.0%) |

| | |
|---|---|
| Diabetic kidney disease | 2(0.7%) |
| **Comorbidities** | |
| Hypertension | 20(6.6%) |
| Dyslipidemia | 98(32.6%) |
| Hypothyroidism | 70(23.3%) |
| Depressive disorders | 14(4.7%) |
| Overweight | 105(34.9%) |
| Obesity | 44(14.6%) |
| **Treatment** | |
| ACEI/ARB | 2(0.7%) |
| Statins | 11(3.6%) |
| Metformin | 14(4.7%) |
| Beta-blockers | 6(2.0%) |
| Levothyroxine | 50(16.6%) |
| antidepressants | 6(2.0%) |
| **Lifestyle and family history** | |
| Current smoker | 76(25.2%) |
| Former smoker | 29(9.6%) |
| Family history of T1DM | 50(16.6%) |
| Family history of diabetes | 116(38.5%) |
| Family history of CVD | 90(29.9%) |
| **Seven-day CGM-derived metrics** | |
| Mean Glucose, mg/dL | 167.15 [143.9 - 195.51] |
| SD, mg/dL | 61.06 [47.89 - 76.07] |
| CV, % | 36.48(7.98) |
| Absolute Glucose Range, mg/dL | 306 [250 - 374] |

| | |
|---|---|
| TBR Level 1, % | 0 [0 - 0.6] |
| TBR Level 2, % | 1.81 [0.38 - 3.9] |
| TIR, % | 59.34 [44.39 - 74.4] |
| TITR, % | 35.68 [24.26 - 47.98] |
| TAR Level 1, % | 23.16 [16.54 - 30.41] |
| TAR Level 2, % | 10.65 [3.25 - 21.62] |
| GRI | 48.19 [30.36 - 68.04] |
| LBGI | 0.6 [0.25 - 1.09] |
| HBGI | 8.42 [4.6 - 12.88] |
| ADRR | 41 [32.83 - 52.11] |
| GMI, % | 7.31 [6.75 - 7.99] |
| MAGE, mg/dL | 115.41 [91.69 - 148.2] |
| GRADE | 9.6 [6.83 - 12.83] |
| GRADE–Euglycemia | 6.74 [3.75 - 13.13] |
| GRADE–Hyperglycemia | 90.5 [82.36 - 95.31] |
| GRADE–Hypoglycemia | 1.5 [0.34 - 4.26] |
| M100, mg/dL | 24.09 [12.12 - 38.88] |
| J-Index | 53.76 [37.71 - 72.51] |
| AUC, mg·min/dL | 165.52 [140.06 - 203.17] |
| MODD, mg/dL | 64.62 [50.16 - 81.48] |
| TBR, % | 1.99 [0.45 - 4.52] |
| TAR, % | 37.92 [21.1 - 53.65] |

Continuous variables are summarized as medians with interquartile ranges or as mean(standard deviation), depending on data distribution. Categorical variables are presented as absolute numbers with corresponding percentages.

**SI conversion factors:** to convert creatinine from mg/dL to µmol/L, multiply by 88.4; to convert total, LDL, HDL, and non-HDL cholesterol from mg/dL to mmol/L, multiply by 0.0259; to convert triglycerides from mg/dL to mmol/L, multiply by 0.0113; to convert glucose

from mg/dL to mmol/L, multiply by 0.0555; to convert eGFR from mL/min to mL/s, multiply by 0.0167.

**Abbreviations:** ACEI – angiotensin-converting enzyme inhibitor, ACR – albumin-to-creatinine ratio, ADRR – average daily risk range, ALT – alanine aminotransferase, ARB – angiotensin receptor blocker, AST – aspartate aminotransferase, BMI – body mass index, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration equation, CRP – C-reactive protein, CSII – continuous subcutaneous insulin infusion, CV – coefficient of variation, CVD – cardiovascular disease, DBP – diastolic blood pressure, DII – daily insulin intake, eGFR – estimated glomerular filtration rate, GRADE – glycemic risk assessment diabetes equation Hb – hemoglobin, HbA1c – glycated hemoglobin, Hct – hematocrit, HDL – high-density lipoprotein cholesterol, IQR – interquartile range, LDL – low-density lipoprotein cholesterol, MAGE – mean amplitude of glycemic excursions, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MPV – mean platelet volume, PLT – platelet count, RDW-CV – red cell distribution width–coefficient of variation, RBC – red blood cell count, SBP – systolic blood pressure, SD – standard deviation, TAR – time above range, TBR – time below range, TIR – time in range, TSH – thyroid-stimulating hormone, WBC – white blood cell count, WHR – waist-to-hip ratio

**Table 2 Spearman correlations between CGM metrics (7 days) and platelet indices**

| **CGM metric** | **MPV** | | **PDW** | | **P-LCR** | |
|---|---|---|---|---|---|---|
| | **R** | ***P*** | **R** | ***P*** | **R** | ***P*** |
| **24-hour CGM metrics** | | | | | | |
| **Mean Glucose, mg/dL** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **SD, mg/dL** | 0.26 | <0.001* | 0.27 | <0.001* | 0.25 | <0.001* |
| **CV, %** | 0.13 | 0.02* | 0.14 | 0.02* | 0.12 | 0.03 |
| **Absolute Glucose Range, mg/dL** | 0.21 | <0.001* | 0.24 | <0.001* | 0.21 | <0.001* |
| **TBR Level 1, %** | 0.00 | 0.96 | 0.00 | 0.94 | -0.01 | 0.90 |

| **TBR Level 2, %** | -0.05 | 0.39 | -0.05 | 0.41 | -0.06 | 0.30 |
|---|---|---|---|---|---|---|
| **TIR, %** | -0.27 | <0.001* | -0.29 | <0.001* | -0.28 | <0.001* |
| **TITR, %** | -0.26 | <0.001* | -0.28 | <0.001* | -0.27 | <0.001* |
| **TAR Level 1, %** | 0.15 | 0.01* | 0.15 | 0.009* | 0.16 | 0.006* |
| **TAR Level 2, %** | 0.29 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **GRI** | 0.27 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
| **LBGI** | -0.10 | 0.10 | -0.09 | 0.10 | -0.10 | 0.07 |
| **HBGI** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **ADRR** | 0.24 | <0.001* | 0.26 | <0.001* | 0.24 | <0.001* |
| **GMI, %** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **MAGE, mg/dL** | 0.20 | <0.001* | 0.21 | <0.001* | 0.20 | <0.001* |
| **GRADE** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **GRADE–Euglycemia** | -0.28 | <0.001* | -0.30 | <0.001* | -0.29 | <0.001* |
| **GRADE–Hyperglycemia** | 0.27 | <0.001* | 0.28 | <0.001* | 0.28 | <0.001* |
| **GRADE–Hypoglycemia** | -0.09 | 0.12 | -0.09 | 0.11 | -0.10 | 0.08 |
| **M100, mg/dL** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **J-Index** | 0.28 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |

| **AUC, mg·min/dL** | 0.23 | <0.001* | 0.21 | <0.001* | 0.22 | <0.001* |
|---|---|---|---|---|---|---|
| **MODD, mg/dL** | 0.23 | <0.001* | 0.24 | <0.001* | 0.23 | <0.001* |
| **TBR, %** | -0.04 | 0.46 | -0.04 | 0.50 | -0.05 | 0.36 |
| **TAR, %** | 0.27 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
| **Daytime CGM metrics** | | | | | | |
| **Daytime Mean Glucose, mg/dL** | 0.27 | <0.001* | 0.28 | <0.001* | 0.28 | <0.001* |
| **Daytime SD, mg/dL** | 0.26 | <0.001* | 0.27 | <0.001* | 0.25 | <0.001* |
| **Daytime CV, %** | 0.15 | 0.01* | 0.16 | 0.006* | 0.14 | 0.02* |
| **Daytime Absolute Glucose Range, mg/dL** | 0.22 | <0.001* | 0.25 | <0.001* | 0.22 | <0.001* |
| **Daytime TBR Level 1, %** | -0.00 | 0.98 | -0.00 | 0.96 | -0.02 | 0.78 |
| **Daytime TBR Level 2, %** | -0.04 | 0.53 | -0.04 | 0.48 | -0.05 | 0.42 |
| **Daytime TIR, %** | -0.27 | <0.001* | -0.28 | <0.001* | -0.27 | <0.001* |
| **Daytime TITR, %** | -0.24 | <0.001* | -0.26 | <0.001* | -0.25 | <0.001* |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Daytime TAR Level 1, %** | 0.16 | 0.007* | 0.15 | 0.007* | 0.17 | 0.004* |
| **Daytime TAR Level 2, %** | 0.29 | <0.001* | 0.30 | <0.001* | 0.29 | <0.001* |
| **Daytime GRI** | 0.27 | <0.001* | 0.29 | <0.001* | 0.27 | <0.001* |
| **Daytime LBGI** | -0.08 | 0.15 | -0.09 | 0.11 | -0.10 | 0.10 |
| **Daytime HBGI** | 0.28 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
| **Daytime ADRR** | 0.25 | <0.001* | 0.26 | <0.001* | 0.24 | <0.001* |
| **Daytime GMI, %** | 0.27 | <0.001* | 0.28 | <0.001* | 0.28 | <0.001* |
| **Daytime MAGE, mg/dL** | 0.21 | <0.001* | 0.22 | <0.001* | 0.21 | <0.001* |
| **Daytime GRADE** | 0.27 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
| **Daytime GRADE–Euglycemia** | -0.28 | <0.001* | -0.30 | <0.001* | -0.29 | <0.001* |
| **Daytime GRADE–Hyperglycemia** | 0.27 | <0.001* | 0.28 | <0.001* | 0.27 | <0.001* |
| **Daytime GRADE–Hypoglycemia** | -0.08 | 0.16 | -0.09 | 0.11 | -0.09 | 0.10 |
| **Daytime M100, mg/dL** | 0.28 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |

| Daytime J-Index | 0.28 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
|---|---|---|---|---|---|---|
| Daytime AUC, mg·min/dL | 0.22 | <0.001* | 0.20 | <0.001* | 0.22 | <0.001* |
| Daytime MODD, mg/dL | 0.22 | <0.001* | 0.23 | <0.001* | 0.22 | <0.001* |
| Daytime TBR, % | -0.03 | 0.61 | -0.03 | 0.55 | -0.04 | 0.48 |
| Daytime TAR, % | 0.27 | <0.001* | 0.28 | <0.001* | 0.27 | <0.001* |
| Nighttime CGM metrics | | | | | | |
| Nighttime Mean Glucose, mg/dL | 0.26 | <0.001* | 0.27 | <0.001* | 0.27 | <0.001* |
| Nighttime SD, mg/dL | 0.24 | <0.001* | 0.26 | <0.001* | 0.24 | <0.001* |
| Nighttime CV, % | 0.08 | 0.14 | 0.09 | 0.10 | 0.08 | 0.17 |
| Nighttime Absolute Glucose Range, mg/dL | 0.22 | <0.001* | 0.23 | <0.001* | 0.21 | <0.001* |
| Nighttime TBR Level 1, % | -0.02 | 0.69 | -0.02 | 0.78 | -0.03 | 0.60 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Nighttime TBR Level 2, %** | -0.05 | 0.38 | -0.05 | 0.35 | -0.06 | 0.31 |
| **Nighttime TIR, %** | -0.23 | <0.001* | -0.25 | <0.001* | -0.24 | <0.001* |
| **Nighttime TITR, %** | -0.22 | <0.001* | -0.23 | <0.001* | -0.22 | <0.001* |
| **Nighttime TAR Level 1, %** | 0.10 | 0.10 | 0.11 | 0.06 | 0.10 | 0.07 |
| **Nighttime TAR Level 2, %** | 0.25 | <0.001* | 0.26 | <0.001* | 0.25 | <0.001* |
| **Nighttime GRI** | 0.22 | <0.001* | 0.23 | <0.001* | 0.22 | <0.001* |
| **Nighttime LBGI** | -0.11 | 0.06 | -0.11 | 0.06 | -0.12 | 0.04 |
| **Nighttime HBGI** | 0.26 | <0.001* | 0.28 | <0.001* | 0.27 | <0.001* |
| **Nighttime ADRR** | 0.22 | <0.001* | 0.24 | <0.001* | 0.22 | <0.001* |
| **Nighttime GMI, %** | 0.26 | <0.001* | 0.27 | <0.001* | 0.27 | <0.001* |
| **Nighttime MAGE, mg/dL** | 0.16 | 0.006* | 0.16 | 0.004* | 0.15 | 0.007* |
| **Nighttime GRADE** | 0.26 | <0.001* | 0.27 | <0.001* | 0.26 | <0.001* |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Nighttime GRADE–Euglycemia** | -0.24 | <0.001* | -0.26 | <0.001* | -0.25 | <0.001* |
| **Nighttime GRADE–Hyperglycemia** | 0.22 | <0.001* | 0.24 | <0.001* | 0.23 | <0.001* |
| **Nighttime GRADE–Hypoglycemia** | -0.11 | 0.06 | -0.11 | 0.06 | -0.12 | 0.04 |
| **Nighttime M100, mg/dL** | 0.27 | <0.001* | 0.28 | <0.001* | 0.27 | <0.001* |
| **Nighttime J-Index** | 0.27 | <0.001* | 0.29 | <0.001* | 0.28 | <0.001* |
| **Nighttime AUC, mg·min/dL** | 0.19 | 0.001* | 0.17 | 0.003* | 0.18 | 0.001* |
| **Nighttime MODD, mg/dL** | 0.23 | <0.001* | 0.24 | <0.001* | 0.22 | <0.001* |
| **Nighttime TBR, %** | -0.06 | 0.28 | -0.06 | 0.28 | -0.07 | 0.22 |
| **Nighttime TAR, %** | 0.23 | <0.001* | 0.25 | <0.001* | 0.24 | <0.001* |

Values are presented as Spearman's correlation coefficients (R) with corresponding p-values. Correlations were calculated for 24-hour, daytime, and nighttime CGM metrics.

* indicates significance after FDR correction (Benjamini–Hochberg), applied per platelet index.

**Abbreviations:** ADRR – average daily risk range, AUC – area under the curve, CGM – continuous glucose monitoring, CV – coefficient of variation, GRI – glucose risk index, HBGI – high blood glucose index, J-Index – J-index of glycemic control, LBGI – low blood glucose index, M100 – M-value (100 mg/dL reference), MAGE – mean amplitude of glycemic excursions, MODD – mean of daily differences, MPV – mean platelet volume, PDW – platelet

distribution width, P-LCR – platelet large cell ratio, SD – standard deviation, TAR – time above range, TBR – time below range, TIR – time in range, TITR – time in tight range

**Table 3. Spearman correlations between platelet indices and non-glycemic variables**

| **Variable** | **MPV** | | **PDW** | | **P-LCR** | |
|---|---|---|---|---|---|---|
| | **R** | ***P*** | **R** | ***P*** | **R** | ***P*** |
| **DII, U/kg** | 0.11 | 0.07 | 0.12 | 0.05 | 0.12 | 0.05 |
| **Diabetes duration, years** | -0.08 | 0.18 | -0.11 | 0.06 | -0.08 | 0.15 |
| **WBC, $\times 10^3$/µL** | -0.06 | 0.28 | -0.06 | 0.27 | -0.08 | 0.19 |
| **RBC, $\times 10^6$/µL** | -0.12 | 0.04 | -0.05 | 0.41 | -0.10 | 0.10 |
| **Hb, g/dL** | -0.07 | 0.22 | -0.01 | 0.88 | -0.05 | 0.35 |
| **Hct, %** | -0.07 | 0.25 | 0.00 | 0.97 | -0.05 | 0.42 |
| **MCV, fL** | 0.13 | 0.02 | 0.12 | 0.03 | 0.13 | 0.03 |
| **MCH, pg** | 0.08 | 0.16 | 0.08 | 0.18 | 0.08 | 0.19 |
| **MCHC, pg** | -0.02 | 0.74 | -0.02 | 0.79 | -0.02 | 0.69 |
| **PLT, $\times 10^3$/µL** | -0.38 | <0.001* | -0.38 | <0.001* | -0.38 | <0.001* |
| **RDW-CV, %** | 0.02 | 0.76 | 0.00 | 0.95 | 0.02 | 0.68 |
| **PCT, %** | -0.02 | 0.78 | -0.03 | 0.60 | -0.02 | 0.68 |
| **ACR [mg/g]** | -0.03 | 0.59 | -0.04 | 0.53 | -0.04 | 0.53 |
| **Sodium, mmol/L** | -0.04 | 0.47 | -0.06 | 0.31 | -0.05 | 0.38 |
| **Potassium, mmol/L** | 0.06 | 0.33 | 0.06 | 0.29 | 0.06 | 0.28 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Total cholesterol, mg/dL** | -0.02 | 0.71 | -0.00 | 0.99 | -0.02 | 0.73 |
| **LDL cholesterol, mg/dL** | -0.04 | 0.52 | -0.01 | 0.86 | -0.03 | 0.59 |
| **HDL cholesterol, mg/dL** | 0.02 | 0.80 | 0.03 | 0.60 | 0.02 | 0.76 |
| **Non-HDL cholesterol, mg/dL** | -0.03 | 0.55 | -0.04 | 0.48 | -0.04 | 0.48 |
| **Triglycerides, mg/dL** | 0.04 | 0.45 | 0.08 | 0.16 | 0.05 | 0.36 |
| **ALT, U/L** | 0.01 | 0.92 | 0.01 | 0.80 | 0.02 | 0.78 |
| **AST, U/L** | 0.03 | 0.60 | 0.03 | 0.56 | 0.04 | 0.48 |
| **Creatinine, mg/dL** | -0.08 | 0.16 | -0.05 | 0.37 | -0.07 | 0.21 |
| **CRP, mg/L** | 0.05 | 0.40 | 0.03 | 0.61 | 0.04 | 0.44 |
| **TSH, µIU/mL** | 0.07 | 0.23 | 0.08 | 0.15 | 0.06 | 0.27 |
| **HbA1c, %** | 0.23 | <0.001* | 0.24 | <0.001* | 0.23 | <0.001* |
| **Height, m** | -0.04 | 0.53 | -0.02 | 0.77 | -0.03 | 0.56 |
| **Body weight, kg** | -0.11 | 0.06 | -0.08 | 0.15 | -0.10 | 0.08 |
| **BMI, kg/m²** | -0.10 | 0.08 | -0.08 | 0.17 | -0.09 | 0.11 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Waist circumference, m** | -0.09 | 0.10 | -0.07 | 0.21 | -0.09 | 0.13 |
| **Hip circumference, m** | -0.09 | 0.12 | -0.09 | 0.12 | -0.09 | 0.13 |
| **SBP, mmHg** | -0.05 | 0.35 | -0.04 | 0.48 | -0.05 | 0.42 |
| **DBP, mmHg** | -0.02 | 0.67 | -0.00 | 0.94 | -0.02 | 0.77 |
| **WHR** | -0.06 | 0.33 | -0.03 | 0.65 | -0.05 | 0.39 |
| **Age, years** | -0.04 | 0.48 | -0.06 | 0.33 | -0.04 | 0.46 |
| **eGFR, mL/min/1.73 m²** | 0.06 | 0.31 | 0.07 | 0.25 | 0.06 | 0.33 |

Values are shown as Spearman's R

* indicates statistical significance after false discovery rate (FDR) correction (Benjamini–Hochberg), applied separately within each platelet index.

**Abbreviations:** ACR – albumin-to-creatinine ratio, ALT – alanine aminotransferase, AST – aspartate aminotransferase, BMI – body mass index, CRP – C-reactive protein, DBP – diastolic blood pressure, DII – daily insulin intake, eGFR – estimated glomerular filtration rate, Hb – hemoglobin, HbA1c – glycated hemoglobin, Hct – hematocrit, HDL – high-density lipoprotein cholesterol, LDL – low-density lipoprotein cholesterol, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, MPV – mean platelet volume, PDW – platelet distribution width, P-LCR – platelet large cell ratio, PLT – platelet count, PCT – plateletcrit, RBC – red blood cell count, RDW-CV – red cell distribution width–coefficient of variation, SBP – systolic blood pressure, TSH – thyroid-stimulating hormone, WBC – white blood cell count, WHR – waist-to-hip ratio

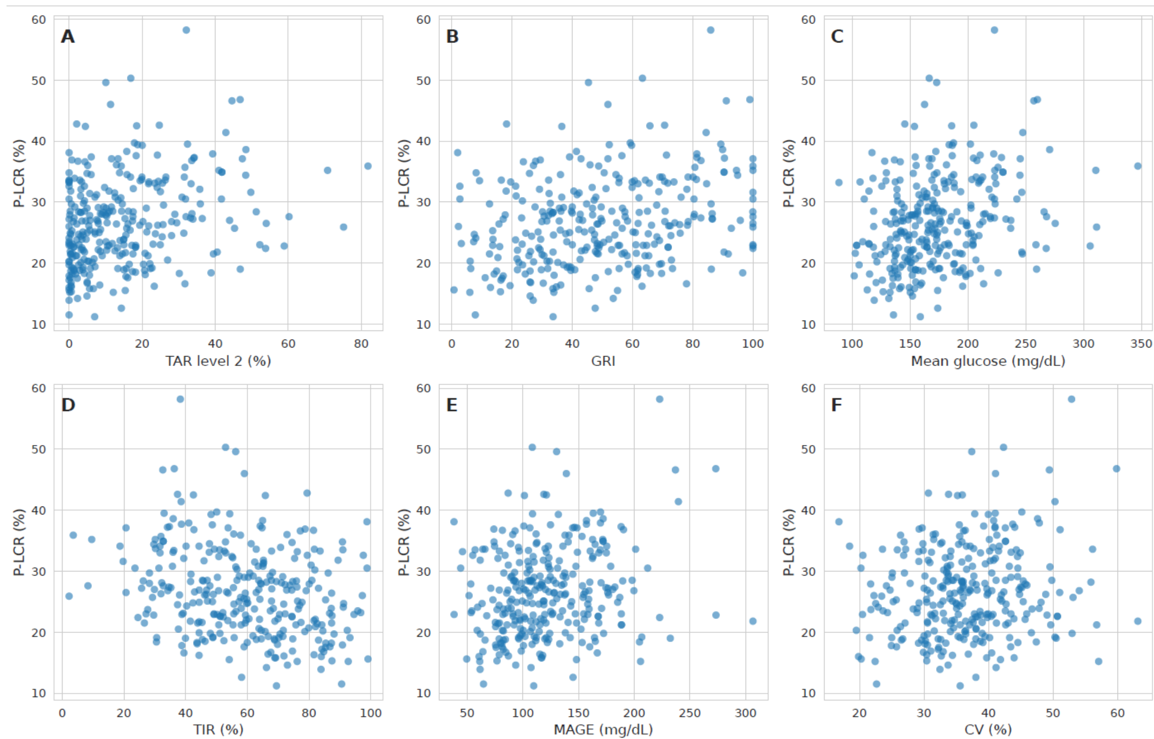


**Figure 1 Unadjusted associations between CGM-derived glycemic metrics and platelet large cell ratio (P-LCR).** Panels **A–F** show scatterplots with linear regression lines and 95% confidence intervals illustrating unadjusted associations between P-LCR (%) and **(A)** TAR level 2 (%), **(B)** glycemic risk index (GRI), **(C)** mean glucose (mg/dL), **(D)** time in range (TIR, %), **(E)** mean amplitude of glycemic excursions (MAGE, mg/dL), and **(F)** coefficient of variation (CV, %)

**Abbreviations:** P-LCR, platelet large cell ratio; CGM, continuous glucose monitoring; TAR, time above range; TIR, time in range; GRI, glycemic risk index; MAGE, mean amplitude of glycemic excursions; CV, coefficient of variation.

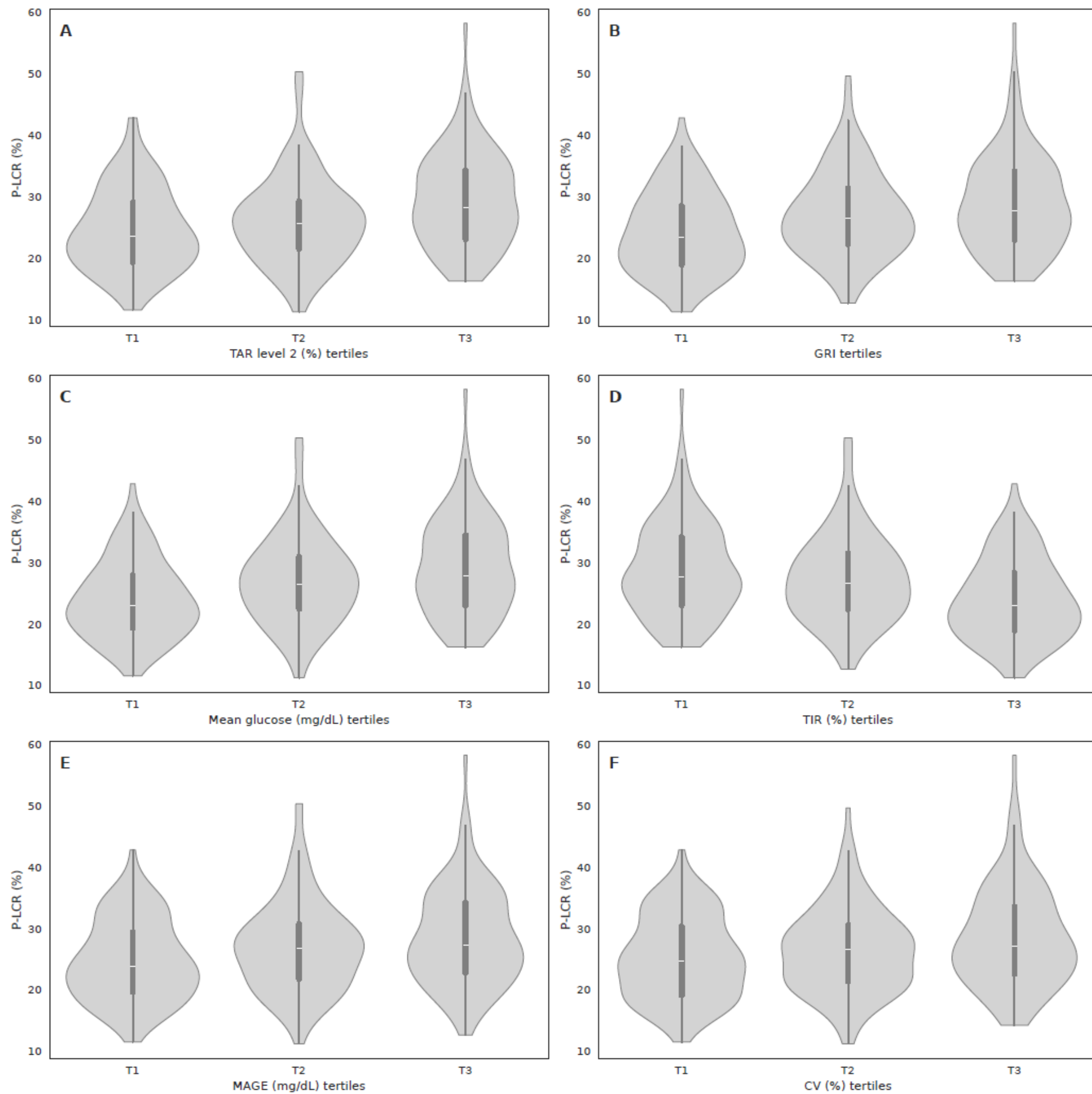


**Figure 2** Violin plots showing platelet large cell ratio (P-LCR) across tertiles of selected continuous glucose monitoring (CGM) metrics: **(A)** TAR level 2 (%), **(B)** glycemic risk index (GRI), **(C)** mean glucose (mg/dL), **(D)** time in range (TIR, %), **(E)** mean amplitude of glycemic excursions (MAGE, mg/dL), and **(F)** coefficient of variation (CV, %). Distributions are presented as violin plots with embedded boxplots indicating the median and interquartile range. CGM metrics were categorized into tertiles (T1–T3) based on their empirical distribution.

**Abbreviations:** P-LCR, platelet large cell ratio; CGM, continuous glucose monitoring; TAR, time above range; TIR, time in range; GRI, glycemic risk index; MAGE, mean amplitude of glycemic excursions; CV, coefficient of variation.

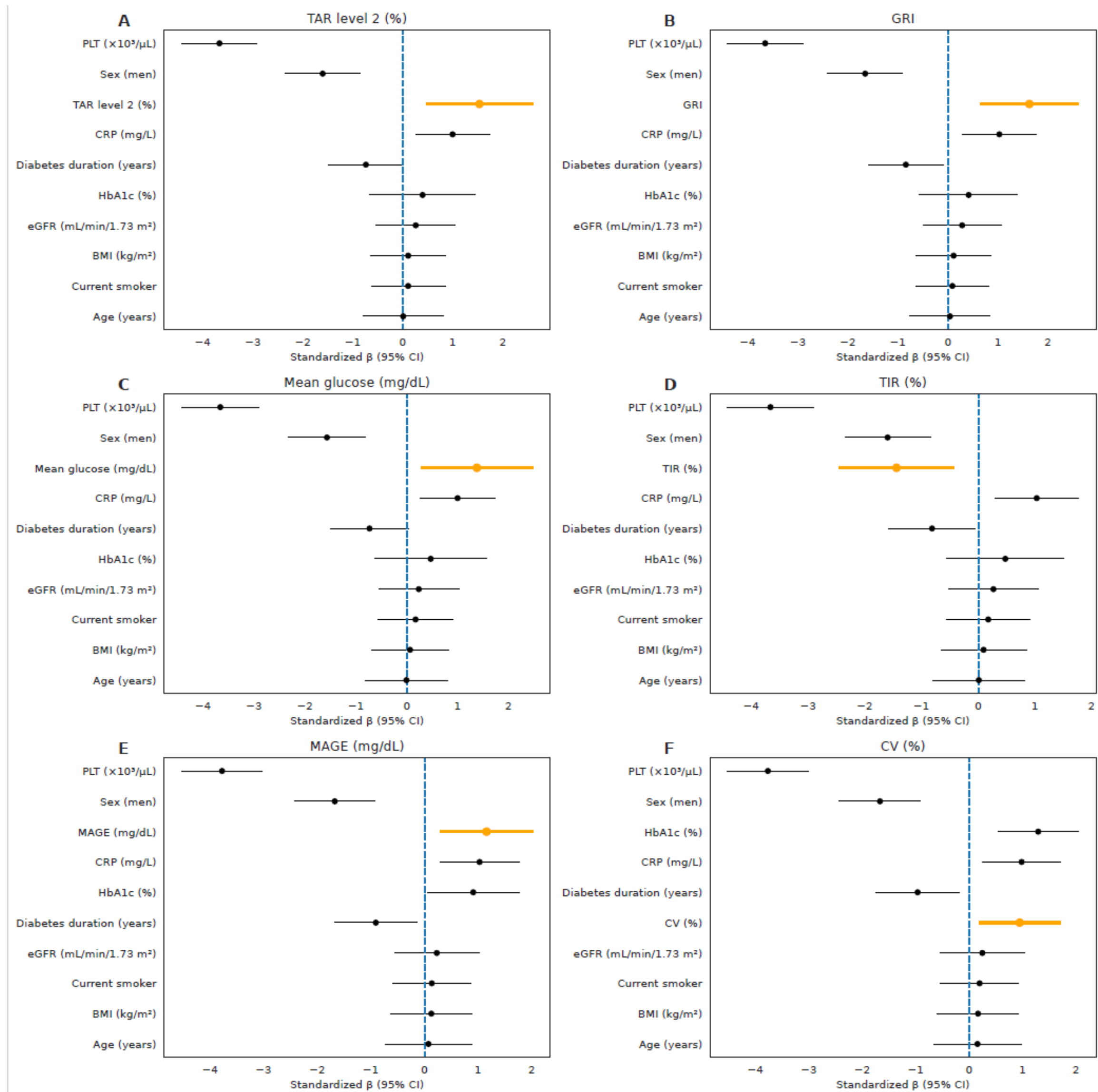


**Figure 3 Multivariable linear regression models showing associations between CGM-derived glycemic metrics and platelet large cell ratio**. Panels **A–F** present standardized regression coefficients (β) with 95% confidence intervals from separate multivariable linear regression models including one CGM-derived parameter each: **(A)** TAR level 2 (%), **(B)** glycemic risk index (GRI), **(C)** mean glucose (mg/dL), **(D)** time in range (TIR, %), **(E)** mean amplitude of glycemic excursions (MAGE, mg/dL), and **(F)** coefficient of variation (CV, %)

Each CGM-derived metric was added separately to the same multivariable base model, including age, sex, BMI, diabetes duration, CRP, eGFR, HbA1c, current smoking, and PLT. CGM-derived parameters are highlighted for clarity. Regression coefficients are standardized to allow comparison of effect sizes across variables.

**Short title:** Glycemic variability and platelet morphology in type 1 diabetes