

Correlation of blood glucose variability with peripheral neuropathy risk in type 2 diabetes patients: a cross-sectional analytical study

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ABSTRACT

Introduction: Blood glucose variability (GV) has emerged as a potential determinant of microvascular complications beyond traditional glycemic markers such as HbA1c. However, evidence regarding its association with diabetic peripheral neuropathy (DPN), particularly in resource-limited settings, remains limited. This study aimed to analyze the correlation between GV and the risk of peripheral neuropathy among patients with type 2 diabetes mellitus (T2DM).

Research Methodology: An analytical cross-sectional study was conducted among 85 patients with T2DM attending primary healthcare facilities in Makassar, Indonesia. Blood glucose variability was assessed using the coefficient of variation (CV), while peripheral neuropathy was evaluated using the Michigan Neuropathy Screening Instrument (MNSI). Bivariate analysis was performed using chi-square and correlation tests, followed by multivariable logistic regression to determine independent associations. Statistical significance was set at $\alpha = 0.05$.

Results: High GV ($CV \geq 36\%$) was significantly associated with peripheral neuropathy in bivariate analysis ($OR = 3.46$; 95% CI: 1.39–8.59; $p = 0.007$). In multivariate analysis, GV remained an independent predictor (adjusted $OR = 2.98$; 95% CI: 1.12–7.91; $p = 0.028$), whereas $HbA1c \geq 7\%$ was not statistically significant ($AOR = 2.67$; 95% CI: 0.92–7.73; $p = 0.071$). Duration of diabetes showed a positive but non-significant association ($AOR = 2.41$; 95% CI: 0.89–6.54; $p = 0.082$).

Conclusion: Blood glucose variability is an independent and clinically relevant predictor of peripheral neuropathy in T2DM patients. These findings support integrating GV assessment into routine diabetes management and highlight the need for strategies to improve glycemic stability and reduce the risk of complications.

Keywords: blood glucose variability; diabetic neuropathies; glycemic control; type 2 diabetes mellitus; risk factors.



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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a major and escalating public health burden, particularly in low- and middle-income countries where health system capacity to manage chronic complications remains constrained (Al Sultan et al., 2026). Among its most debilitating sequelae, diabetic peripheral neuropathy (DPN) affects up to 50% of patients and is a leading cause of foot ulceration, amputation, and reduced quality of life (Aldafas et al., 2026). Despite advances in glycemic management, the incidence of DPN remains high, suggesting that conventional markers such as glycated hemoglobin (HbA1c) may not fully capture the complexity of glycemic exposure relevant to neural damage (Battelino et al., 2025). This gap has prompted increased attention to blood glucose variability (GV) as a potentially critical yet under-recognized determinant of microvascular complications (Chen et al., 2025).

Emerging evidence indicates that GV, commonly quantified using metrics such as standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE), may exert independent pathophysiological effects beyond sustained hyperglycemia (Crowards et al., 2025). Mechanistically, fluctuations in glucose levels have been associated with increased oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways, all of which contribute to neuronal injury (Cutruzzola et al., 2024). Several observational studies have reported significant associations between higher GV and markers of peripheral nerve dysfunction, including reduced nerve conduction velocity and increased neuropathic symptom scores (De et al., 2026). Furthermore, continuous glucose monitoring (CGM)-based studies suggest that short-term glycemic excursions may be more strongly correlated with microvascular damage than average glucose levels alone (Formichi et al., 2025).

However, the current body of literature remains heterogeneous and methodologically limited. Many studies rely on cross-sectional designs, limiting causal inference, while others use inconsistent GV metrics, making comparisons difficult (Gandecka-Pempera et al., 2025). Additionally, a substantial proportion of studies are conducted in high-income settings with advanced monitoring technologies, reducing generalizability to routine clinical contexts, particularly in resource-limited environments (Gu et al., 2024). Importantly, few studies have simultaneously controlled for key confounders such as diabetes duration, comorbidities, and treatment regimens, which may bias the observed associations. Evidence specific to Southeast Asian populations, including Indonesia, is particularly scarce despite the region's rapidly growing diabetes burden (Junquera-Godoy et al., 2025).

This study addresses these gaps by examining the relationship between blood glucose variability and the risk of peripheral neuropathy in patients with T2DM using a robust analytical framework. By integrating standardized GV metrics and clinically validated neuropathy assessments, this research aims to provide more consistent, contextually relevant evidence. Furthermore, the study incorporates multivariable modeling to account for key confounding factors, thereby strengthening the validity of the findings.

The novelty of this study lies in its focus on GV as an independent predictor of DPN within a real-world clinical setting, rather than relying solely on HbA1c as the primary glycemic indicator. Additionally, this research contributes region-specific evidence that may enhance the applicability of findings to similar healthcare contexts. By emphasizing variability rather than average glycemic control, the study challenges prevailing paradigms in diabetes management and supports a more nuanced understanding of glycemic risk profiles. Therefore, the primary objective of this study is to analyze the correlation between blood glucose variability and the risk of peripheral neuropathy in patients with type 2 diabetes mellitus. Specifically, the study aims to

(1) quantify GV using established metrics, (2) assess the prevalence and severity of peripheral neuropathy, and (3) determine the independent association between GV and neuropathy risk after adjusting for relevant clinical covariates. Ultimately, the findings are expected to inform more targeted strategies for risk stratification and intervention in diabetes care.

RESEARCH METHODOLOGY

Study Design

This study employed an analytical observational design with a cross-sectional approach. This design was selected to evaluate the association between blood glucose variability (GV) and peripheral neuropathy risk in patients with type 2 diabetes mellitus (T2DM) within a defined time frame. The cross-sectional design is appropriate for identifying correlations and estimating prevalence in clinical settings where longitudinal follow-up is not feasible.

Setting and Participants

The study was conducted at selected primary healthcare facilities and outpatient clinics in Makassar, South Sulawesi, Indonesia, between January and March 2026.

Inclusion Criteria: Patients diagnosed with T2DM for at least one year. Age ≥ 30 years. Receiving routine diabetes care. Willing to participate and provide informed consent

Exclusion Criteria: Patients with type 1 diabetes or gestational diabetes. History of neurological disorders unrelated to diabetes. Severe comorbid conditions (e.g., advanced renal failure, malignancy). Incomplete clinical or laboratory data

Sampling Technique

A consecutive sampling method was applied to recruit eligible participants who met the inclusion criteria during the study period. The sample size was determined using a correlation study formula with a confidence level of 95% and statistical power of 80%. Based on an expected moderate correlation ($r = 0.30$) between GV and neuropathy risk, the minimum required sample size was 85 participants.

Variables and Measurement

Independent Variable

Blood glucose variability (GV) was defined as fluctuations in blood glucose levels over time. GV was quantified using: Standard deviation (SD). Coefficient of variation (CV). Mean amplitude of glycemic excursions (MAGE)

Dependent Variable

Peripheral neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI), which included both a questionnaire and a physical examination component. A validated cut-off score was used to classify neuropathy risk.

Covariates

Covariates included age, sex, duration of diabetes, body mass index (BMI), HbA1c level, comorbidities (hypertension, dyslipidemia), and medication use.

Validity and Reliability

The MNSI instrument has demonstrated good validity and reliability in previous studies, with Cronbach's $\alpha > 0.80$. Calibration of glucometers and standard laboratory procedures ensured measurement accuracy.

Data Source

Primary data were collected through patient interviews, clinical examinations, and laboratory measurements. Secondary data were obtained from medical records.

Data Collection

Data collection was conducted by trained healthcare professionals following standardized procedures. Blood glucose measurements were obtained from patient records or monitored over a specified period. Neuropathy assessment was performed using the MNSI protocol. Quality Control Training and data collector standardization. Pre-testing of instruments. Double data entry and verification. Routine calibration of measurement tools

Data Analysis

Data were analyzed using IBM SPSS Statistics version 26.0. Descriptive Analysis Descriptive statistics were used to summarize participant characteristics, including means, standard deviations, frequencies, and percentages. Bivariate Analysis. The association between GV and peripheral neuropathy was analyzed using Pearson or Spearman correlation tests, depending on data distribution. Chi-square tests were used for categorical variables. Multivariate Analysis. Multivariable logistic regression analysis was performed to determine the independent association between GV and neuropathy risk while adjusting for potential confounders. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were reported. A significance level of $\alpha = 0.05$ was applied for all statistical tests.

Ethical Approval

This study was approved by the Health Research Ethics Committee of Sekolah Tinggi Ilmu Kesehatan Makassar, South Sulawesi, Indonesia, with approval number 225/KEPK/IV/2025. All participants provided written informed consent before enrollment. Confidentiality and anonymity of participant data were strictly maintained throughout the study.

RESULT

A total of 85 patients with type 2 diabetes mellitus were included in the analysis. The baseline characteristics of participants are presented to describe the demographic and clinical profile of the study population. Subsequent analyses examined the distribution of blood glucose variability (GV) metrics and the prevalence of peripheral neuropathy. Bivariate analysis was conducted to explore the relationship between GV and peripheral neuropathy, followed by multivariable logistic regression to identify independent predictors while controlling for potential confounders. The results are presented in a structured manner, including descriptive statistics, correlation analysis, and adjusted effect estimates with corresponding confidence intervals.

Table 1. Characteristics of Respondents (n = 85)

Variable	Category	n (%) / Mean ± SD
Age (years)		56.8 ± 9.4
Sex	Male	38 (44.7%)
	Female	47 (55.3%)
Duration of T2DM	<5 years	29 (34.1%)
	≥5 years	56 (65.9%)
HbA1c (%)		8.2 ± 1.3
BMI (kg/m²)		26.1 ± 3.8
Hypertension	Yes	49 (57.6%)
Dyslipidemia	Yes	42 (49.4%)
Peripheral Neuropathy	Yes	37 (43.5%)

The majority of participants were female (55.3%) with a mean age of 56.8 years. Most had diabetes duration ≥5 years (65.9%) and suboptimal glycemic control (mean HbA1c 8.2%). The prevalence of peripheral neuropathy was 43.5%, indicating a substantial burden of complications in this population.

Table 2. Bivariate Analysis of Blood Glucose Variability and Peripheral Neuropathy

Variable	Neuropathy (Yes) n (%)	Neuropathy (No) n (%)	OR (95% CI)	p-value
High GV (CV ≥36%)	25 (67.6%)	18 (37.5%)	3.46 (1.39–8.59)	0.007
Duration ≥5 years	29 (78.4%)	27 (56.3%)	2.79 (1.05–7.39)	0.039
HbA1c ≥7%	31 (83.8%)	30 (62.5%)	3.08 (1.05–9.04)	0.041
Hypertension	24 (64.9%)	25 (52.1%)	1.70 (0.71–4.08)	0.234

Bivariate analysis showed that high blood glucose variability (CV ≥36%) was significantly associated with peripheral neuropathy (OR = 3.46; 95% CI: 1.39–8.59; p = 0.007). Longer duration of diabetes and poor glycemic control (HbA1c ≥7%) were also significantly associated with neuropathy. Hypertension was not significantly associated.

Table 3. Multivariate Logistic Regression Analysis

Variable	Adjusted OR (95% CI)	p-value
High GV (CV $\geq 36\%$)	2.98 (1.12–7.91)	0.028
Duration ≥ 5 years	2.41 (0.89–6.54)	0.082
HbA1c $\geq 7\%$	2.67 (0.92–7.73)	0.071

After adjusting for confounding variables, high blood glucose variability remained an independent predictor of peripheral neuropathy (AOR = 2.98; 95% CI: 1.12–7.91; $p = 0.028$). Duration of diabetes and HbA1c showed positive associations but were not statistically significant in the adjusted model. These findings suggest that glycemic variability may play a more critical role than average glycemic control in the development of neuropathy. High blood glucose variability was consistently associated with increased risk of peripheral neuropathy across both bivariate and multivariate analyses. The effect size remained clinically meaningful after adjustment, reinforcing GV as an independent risk factor.

DISCUSSION

This study provides robust evidence that blood glucose variability (GV) is independently associated with peripheral neuropathy risk among patients with type 2 diabetes mellitus (T2DM). Notably, GV demonstrated a stronger, statistically significant association than HbA1c in the adjusted model, suggesting that dynamic glycemic fluctuations may be a more sensitive predictor of neuropathic complications than mean glycemic exposure alone. These findings reinforce the growing recognition that glycemic instability constitutes a distinct and clinically relevant dimension of metabolic dysregulation.

The relationship between GV and diabetic peripheral neuropathy (DPN) can be interpreted through multiple interrelated biological mechanisms (Kulecki et al., 2025). Oscillating glucose levels have been shown to induce intermittent spikes in oxidative stress that exceed those observed under sustained hyperglycemia (Lan et al., 2026). This phenomenon leads to endothelial dysfunction, activation of protein kinase C pathways, and increased production of advanced glycation end products (AGEs), all of which contribute to microvascular damage and impaired neural perfusion. Furthermore, the concept of “metabolic memory” provides an additional explanatory layer (Mansour et al., 2025). Repeated glycemic excursions may trigger persistent epigenetic modifications, sustaining inflammatory and oxidative pathways even after glycemic normalization. This mechanism suggests that GV is not merely a concurrent marker but may have cumulative and lasting pathogenic effects on peripheral nerve integrity (Pantazopoulos et al., 2025).

The present findings are consistent with recent international studies demonstrating that GV is associated with microvascular complications, including neuropathy, retinopathy, and nephropathy (Sheen et al., 2025). Large-scale cohort studies and continuous glucose monitoring (CGM)-based analyses have reported that metrics such as coefficient of variation (CV) and mean amplitude of glycemic excursions (MAGE) are significantly correlated with nerve conduction abnormalities and neuropathy severity (Soe & Selvarajah, 2025).

However, evidence from Southeast Asia remains comparatively limited. This study provides important regional data, particularly in the Indonesian context, where diabetes prevalence is rapidly increasing but access to advanced monitoring technologies, such as CGM, remains constrained (Srivastava et al., 2025). The observed association in a real-world clinical setting enhances the external validity and applicability of GV as a risk marker in resource-limited environments (Syaharuddin et al., 2025).

The convergence between this study and prior literature lies in the consistent identification of GV as a significant determinant of diabetic complications (Xin et al., 2025). The magnitude and direction of the association observed align with previous studies, supporting the biological plausibility of the findings. In contrast, divergence emerges in the relative role of HbA1c, which did not retain statistical significance in the multivariable model (Yamaguchi et al., 2024). This finding challenges the conventional paradigm that positions HbA1c as the primary predictor of

microvascular complications. One plausible explanation is that HbA1c reflects average glycemia but fails to capture acute glycemic excursions that may exert disproportionate oxidative and inflammatory effects (Yang et al., 2026). Additionally, modern therapeutic regimens may stabilize HbA1c while allowing residual variability, thereby attenuating its predictive utility in certain populations (Zellers et al., 2026).

The implications of these findings are both clinical and systemic. Clinically, they support a paradigm shift from a unidimensional focus on HbA1c toward a more comprehensive assessment of glycemic patterns, including variability metrics (Zhang et al., 2024). Incorporating GV into routine clinical evaluation may improve early identification of patients at high risk for neuropathy and enable more personalized therapeutic strategies (Ziori et al., 2026). At the health system level, these findings highlight the need to integrate structured glucose monitoring approaches into standard diabetes care (Zulfiah et al., 2025). While CGM remains the gold standard, simplified indicators such as CV derived from self-monitoring data may offer a pragmatic alternative in low-resource settings. Furthermore, clinical guidelines may need to evolve to incorporate GV thresholds into risk-stratification frameworks (Zúnica-García et al., 2024).

Strengths and Limitations

This study has several notable strengths. It provides context-specific evidence from an underrepresented population, applies standardized and clinically relevant measures of GV and neuropathy, and employs multivariable modeling to address confounding. These elements enhance both internal validity and translational relevance. However, limitations should be considered. The cross-sectional design precludes causal inference and limits the ability to establish temporal relationships. The relatively modest sample size may affect statistical power and generalizability. Additionally, using intermittent glucose measurements rather than CGM may underestimate true variability. Residual confounding from unmeasured variables, including dietary patterns and medication adherence, cannot be fully excluded.

CONCLUSION

This study demonstrates that blood glucose variability (GV) is significantly associated with an increased risk of peripheral neuropathy among patients with type 2 diabetes mellitus (T2DM). Importantly, GV remained an independent predictor after adjustment for conventional risk factors, including HbA1c and diabetes duration. These findings indicate that glycemic fluctuations, rather than average glycemic control alone, play a critical role in the development of diabetic peripheral neuropathy. The results provide empirical support for expanding the current paradigm of diabetes management to include GV as a key clinical indicator. Routine assessment of GV using practical measures, such as the coefficient of variation (CV), should be integrated into standard care to improve early detection of high-risk patients. Clinicians are encouraged to adopt individualized therapeutic strategies aimed not only at lowering HbA1c but also at minimizing glycemic excursions. At the policy level, diabetes management guidelines should incorporate GV-based risk stratification and promote access to structured glucose monitoring, particularly in resource-limited settings. Strengthening monitoring systems and clinical decision-making frameworks based on GV may enhance complication prevention and improve long-term patient outcomes.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of Sekolah Tinggi Ilmu Kesehatan Makassar, South Sulawesi, Indonesia (Approval No. 225/KEPK/IV/2025). Written informed consent was obtained from all participants before data collection. Participant confidentiality and anonymity were strictly maintained throughout the study.

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This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

Rusli Rusli: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Maria Kurni Menga: Investigation, Data curation, Validation, Writing – review & editing.

Nurlina Nurlina: Methodology, Investigation, Data curation, Writing – review & editing.

Sara Palander: Formal analysis, Validation, Writing – review & editing.

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Declaration of Generative AI Use

Generative artificial intelligence tools were used to support language refinement and improve clarity of expression during manuscript preparation. All conceptual development, data analysis, interpretation of findings, and final content decisions were performed by the author. The author takes full responsibility for the accuracy and integrity of the work.

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