British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(5): 54062
https://doi.org/10.31083/BJHM54062

Article

Factors Associated With Glycemic Variability in Hospitalized Patients With Type 2 Diabetes Mellitus and Heart Failure

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Academic Editor: John Alcolado
Submitted: 28 October 2025 Revised: 18 December 2025 Accepted: 26 December 2025 Published: 20 May 2026

Abstract

Aims/Background: Patients with concomitant heart failure (HF) and type 2 diabetes mellitus (T2DM) are at high risk for adverse clinical outcomes. Glycemic variability (GV) has emerged as a crucial metric for assessing dysglycemia. However, its determinants in this specific patient population remain poorly characterized. This study aimed to investigate factors associated with GV in hospitalized patients with HF and T2DM. **Methods**: A total of 150 patients hospitalized with T2DM and HF were enrolled. Clinical and laboratory data were collected, and multiple linear regression analysis was performed to identify independent factors associated with four GV indices: standard deviation of blood glucose (SDBG), coefficient of variation (CV), mean of daily differences (MODD), and mean amplitude of glycemic excursions (MAGE). **Results**: Multivariate analysis revealed that C-peptide level was significantly negatively associated with all four GV indices (SDBG: $\beta = –0.219$, $p < 0.001$; log(CV): $\beta = –0.080$, $p < 0.001$; MODD: $\beta = –0.176$, $p < 0.001$; MAGE: $\beta = –0.284$, $p < 0.001$). Age showed significant positive associations with SDBG ($\beta = 0.020$, $p < 0.001$), log(CV) ($\beta = 0.009$, $p < 0.001$), and MODD ($\beta = 0.027$, $p < 0.001$). Diabetes duration was significantly positively associated with SDBG ($\beta = 0.028$, $p < 0.001$), log(CV) ($\beta = 0.011$, $p < 0.001$), and MODD ($\beta = 0.029$, $p < 0.001$). Glycated hemoglobin (HbA1c) was significantly positively associated with SDBG ($\beta = 0.062$, $p = 0.002$), MODD ($\beta = 0.125$, $p < 0.001$), and MAGE ($\beta = 0.196$, $p < 0.001$). Log-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) (log(NT-proBNP)) was significantly positively associated with all GV indices (SDBG: $\beta = 0.085$, $p = 0.002$; log(CV): $\beta = 0.046$, $p = 0.002$; MODD: $\beta = 0.090$, $p = 0.009$; MAGE: $\beta = 0.162$, $p = 0.003$). Additionally, family history of diabetes was positively associated with SDBG ($\beta = 0.184$, $p = 0.001$), log(CV) ($\beta = 0.088$, $p = 0.004$), and MODD ($\beta = 0.175$, $p = 0.012$). A history of cardiovascular disease was positively associated with MAGE ($\beta = 0.265$, $p = 0.024$). Body mass index (BMI) was negatively associated with MODD ($\beta = –0.036$, $p < 0.001$) but positively associated with MAGE ($\beta = 0.037$, $p = 0.007$). The regression models explained 34.9% to 49.6% of the variance across the different GV indices. **Conclusion**: Glycemic variability in hospitalized patients with T2DM and HF is influenced by multiple clinical and metabolic factors. C-peptide level, age, diabetes duration, HF severity (reflected by NT-proBNP), and overall glycemic control are primary factors associated with GV. These findings suggest that clinical management should adopt individualized strategies that account for the heterogeneity and distinct characteristics of different GV indices.

Keywords: diabetes mellitus; heart failure; glycemic variability; blood glucose

1. Introduction

Type 2 diabetes mellitus (T2DM) and heart failure (HF) represent two major global health challenges, with significant epidemiological overlap and a complex pathophysiological interplay [1]. The coexistence of these conditions is associated with worse clinical outcomes compared with either condition alone, exerting synergistic detrimental effects on overall prognosis [2]. Recent epidemiological data indicate that approximately 30–40% of patients with heart failure also have T2DM, while the prevalence of HF among patients with diabetes ranges from 10% to 30%, depending on age and comorbidities [3]. This bidirectional relationship is driven by shared risk factors and intricate mechanistic pathways.

Although glycated hemoglobin (HbA1c) has traditionally served as the cornerstone of glycemic assessment in diabetes management, accumulating evidence suggests that glycemic variability (GV) may provide additional prognostic information beyond mean glucose levels. Glycemic variability refers to the magnitude, frequency, and duration of glucose fluctuations within and between days, representing a dynamic component of glucose homeostasis [4]. A growing body of evidence indicates that increased GV is independently associated with adverse outcomes in diabetic and cardiovascular populations, including microvascular complications, cardiovascular events, and increased risk of mortality [4,5].

The assessment and management of GV are of particular clinical relevance in patients with concomitant T2DM and HF. Heart failure can influence glucose metabolism through multiple mechanisms, including tissue hypoxia, neurohormonal activation, altered gastrointestinal absorption, and reduced physical activity [6]. Conversely, GV may exacerbate HF through mechanisms such as fluid re-

tention, electrolyte imbalance, and direct myocardial toxicity [7]. These reciprocal interactions may create a vicious cycle in which HF worsens glycemic control, and unstable glycemia further aggravates cardiac dysfunction, ultimately contributing to higher rates of hospitalization and mortality [8].

Despite the significant clinical implications of GV in this high-risk population, current understanding of the factors influencing different GV parameters in patients with T2DM and HF remains limited. Most previous studies have focused on single GV metrics or evaluated diabetic populations without specifically accounting for heart failure status [9,10]. Furthermore, different GV indices capture distinct dimensions of glucose fluctuations: standard deviation of blood glucose (SDBG) reflects overall dispersion, the coefficient of variation (CV) represents relative variability, the mean amplitude of glycemic excursions (MAGE) captures major glucose swings, and the mean of daily differences (MODD) indicates day-to-day variability [11]. Whether these indices share common determinants or are influenced by distinct factors in patients with HF warrants systematic investigation.

Identifying potentially modifiable factors associated with GV in patients with T2DM and HF may inform targeted interventions aimed at improving glycemic stability and, potentially, clinical outcomes. Therefore, the present study aimed to comprehensively evaluate factors associated with four GV indices (SDBG, CV, MODD, and MAGE) in hospitalized patients with T2DM and HF using multiple linear regression analysis. Elucidating these associations may contribute to the development of personalized glycemic management strategies for this vulnerable population.

2. Methods

2.1 Patients

This retrospective cohort study consecutively enrolled 150 hospitalized patients with concomitant T2DM and HF from People's Hospital of Baishan between January 2022 and December 2023. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association (ADA) criteria [12], while HF was diagnosed based on the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure [13].

The inclusion criteria were as follows: (1) a confirmed diagnosis of T2DM; (2) a confirmed diagnosis of HF; (3) age $\geq$18 years; and (4) availability of complete capillary blood glucose monitoring data for the assessment of GV. The exclusion criteria included: (1) acute coronary syndrome within the preceding 3 months; (2) severe hepatic insufficiency or end-stage renal disease requiring renal replacement therapy; (3) active malignancy or other life-limiting conditions; and (4) pregnancy or lactation.

The study protocol was approved by the Ethics Committee of People's Hospital of Baishan (approval number: KY2025023). The study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was waived by the Ethics Committee of People's Hospital of Baishan due to the retrospective study design and the anonymization of all patient data.

2.2 Data Collection

Comprehensive clinical data were systematically extracted from the electronic medical record system. Demographic variables included age and gender. Height and weight measured at hospital admission were used to calculate body mass index (BMI, kg/m^2). Disease-related variables included duration of T2DM, family history of diabetes, and history of hypertension. History of cardiovascular disease (CVD) was extracted from the electronic medical record system and defined as any prior diagnosis of CVD other than the current episode of heart failure, including coronary artery disease, myocardial infarction, stroke, or peripheral arterial disease. To comprehensively assess cardiac status, we used the New York Heart Association (NYHA) classification to assess cardiac function in patients with heart failure [14] and collected N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, which are recognized biomarkers for the diagnosis and assessment of prognosis of heart failure [15].

Renal function parameters included the estimated glomerular filtration rate (eGFR). Glycemic parameters included HbA1c and fasting C-peptide levels. NT-proBNP levels were measured using an electrochemiluminescence immunoassay on a cobas e 411 analyzer (Roche Diagnostics, Basel, Switzerland). Capillary blood glucose monitoring was performed using the Accu-Chek Inform II system (Roche Diagnostics, Basel, Switzerland). HbA1c was determined by high-performance liquid chromatography using the VARIANT™ II Hemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA, USA).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine levels. Serum creatinine was measured using an enzymatic method on an ADVIA 2400 Chemistry System (Siemens Healthineers, Erlangen, Germany). Fasting serum C-peptide concentrations were quantified by an electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland).

2.3 Assessment of Glycemic Variability Indices

GV indices were calculated using capillary blood glucose monitoring data obtained over at least 72 hours during hospitalization. All patients adhered to a standardized seven-point daily glucose monitoring protocol, with measurements obtained at each of the three meals, 2 hours after each meal, and at bedtime. This protocol ensured a minimum of 21 glucose values per patient for subsequent analy-

Table 1. Baseline clinical characteristics of the study population.

Variable	Summary
Age (years)	67.81 ± 7.60
Body mass index (kg/m^2)	28.31 ± 4.04
Diabetes duration (years)	11.87 ± 5.73
Estimated glomerular filtration rate (mL/min/1.73 m^2)	66.03 ± 21.23
NT-proBNP (pg/mL)	3183.50 (1383.00–6764.00)
HbA1c (%)	8.47 ± 1.40
C-peptide (ng/mL)	1.58 ± 0.72
Standard deviation of blood glucose, SDBG (mmol/L)	1.51 ± 0.44
Coefficient of variation of blood glucose, CV (%)	18.69 ± 4.53
Mean of daily differences, MODD (mmol/L)	1.78 ± 0.56
Mean amplitude of glycemic excursions, MAGE (mmol/L)	4.05 ± 0.79
Gender, n (%)	
Female	44 (29.3)
Male	106 (70.7)
Heart failure phenotype, n (%)	
HFrEF	39 (26.0)
HFpEF	111 (74.0)
NYHA functional class, n (%)	
Class I	0 (0.0)
Class II	67 (44.7)
Class III	53 (35.3)
Class IV	30 (20.0)
Hypertension, n (%)	
No	34 (22.7)
Yes	116 (77.3)
Family history of diabetes, n (%)	
No	78 (52.0)
Yes	72 (48.0)
History of cardiovascular disease, n (%)	
No	103 (68.7)
Yes	47 (31.3)

NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, glycated hemoglobin; HFrEF, Heart Failure with reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; NYHA, New York Heart Association; SDBG, standard deviation of blood glucose; CV, coefficient of variation; MODD, mean of daily differences; MAGE, mean amplitude of glycemic excursions.

sis. All GV indices were computed using standardized and previously validated algorithms.

The GV indices evaluated include the following: the standard deviation of blood glucose (SDBG), which represents the overall dispersion of glucose values around the mean; the coefficient of variation (CV), calculated as (SDBG / mean glucose) × 100%, indicating relative variability independent of mean glucose levels; the mean of daily differences (MODD), which reflects day-to-day glycemic variability by averaging the absolute differences between corresponding time points on consecutive days; and the mean amplitude of glycemic excursions (MAGE), which quantifies the magnitude of major glucose fluctuations by calculating the arithmetic mean of glucose excursions exceeding one standard deviation of the mean.

The selection of these four GV indices for multivariate analysis was based on their established utility in capturing distinct and complementary dimensions of glucose fluctuations [16–18]. Both SDBG and CV are widely used measures of overall variability, with CV providing normalization for differences in mean glucose levels. MODD was included to specifically assess day-to-day glycemic stability, which is particularly relevant in the hospitalized setting [19]. MAGE was included because it is considered the gold standard for capturing major acute glucose excursions (peaks and nadirs), which are hypothesized to exert particularly detrimental effects on the vascular endothelium [7]. By employing this comprehensive set of indices, we aimed to provide a more complete assessment of the factors influencing different aspects of GV in this patient population.

Table 2. Multivariate linear regression analysis of factors associated with SDBG.

Variable	β coefficient	SE	*t*-value	*p*-value	95% CI (lower)	95% CI (upper)
Age	0.020	0.004	5.362	<0.001	0.012	0.027
Gender	–0.036	0.059	–0.611	0.542	–0.154	0.081
BMI	–0.006	0.007	–0.852	0.396	–0.019	0.007
NYHA class III	0.009	0.059	0.156	0.876	–0.108	0.126
NYHA class IV	–0.042	0.073	–0.572	0.568	–0.187	0.103
Diabetes duration	0.028	0.005	5.966	<0.001	0.018	0.037
Hypertension	0.042	0.065	0.651	0.516	–0.086	0.171
eGFR	0.002	0.001	1.478	0.142	–0.001	0.004
Log(NT-proBNP)	0.085	0.027	3.187	0.002	0.032	0.138
Family history of diabetes	0.184	0.054	3.413	0.001	0.078	0.291
Cardiovascular disease history	0.031	0.057	0.546	0.586	–0.082	0.144
HbA1c	0.062	0.019	3.209	0.002	0.024	0.100
C-peptide	–0.219	0.037	–5.879	<0.001	–0.293	–0.145

Note: BMI, body mass index; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, glycated hemoglobin; CI, confidence interval; SE, standard error.

Table 3. Multivariate linear regression analysis of factors associated with log(CV).

Variable	β coefficient	SE	*t*-value	*p*-value	95% CI (lower)	95% CI (upper)
Age	0.009	0.002	4.321	<0.001	0.005	0.013
Gender	–0.026	0.033	–0.79	0.431	–0.091	0.039
BMI	0.000	0.004	0.127	0.899	–0.007	0.008
NYHA class III	0.021	0.033	0.649	0.517	–0.043	0.086
NYHA class IV	–0.037	0.041	–0.913	0.363	–0.117	0.043
Diabetes duration	0.011	0.003	4.449	<0.001	0.006	0.016
Hypertension	0.047	0.036	1.301	0.195	–0.024	0.118
eGFR	0.001	0.001	1.792	0.075	0.000	0.003
Log(NT-proBNP)	0.046	0.015	3.148	0.002	0.017	0.076
Family history of diabetes	0.088	0.03	2.954	0.004	0.029	0.147
Cardiovascular disease history	–0.006	0.032	–0.194	0.847	–0.069	0.056
HbA1c	–0.015	0.011	–1.367	0.174	–0.036	0.006
C-peptide	–0.080	0.021	–3.865	<0.001	–0.120	–0.039

Note: BMI, body mass index; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, glycated hemoglobin; CI, confidence interval.

2.4 Statistical Analysis

All statistical analyses were performed using R software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) [20]. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median (interquartile range) [M (IQR)]. Categorical variables are presented as frequencies and percentages [n (%)].

Multiple linear regression analysis was conducted to examine independent associations between clinical factors and each GV index (SDBG, CV, MODD, and MAGE). All independent variables listed in Table 1 were included in the initial regression models based on clinical relevance and prior evidence, rather than through univariate prescreening. To satisfy the assumptions of linear regression, residual normality was formally evaluated using the Shapiro-Wilk test. Based on these assessments, natural logarithmic transformation was applied to CV (W = 0.9623, $p < 0.001$ for untransformed CV; W = 0.988, $p = 0.223$ after log transformation), while SDBG, MODD, and MAGE were analyzed without transformation, as their residuals met normality assumptions (all $p > 0.05$).

Multicollinearity among independent variables was assessed using variance inflation factors (VIFs) and tolerance values. All predictors had VIF values <5 (range: 1.031–1.154) with tolerance values >0.20, indicating no significant multicollinearity among predictors and acceptable model stability.

The regression coefficients (β) reported in the final results tables represent non-standardized coefficients. For the log-transformed CV model, coefficients represent the change in log(CV) per unit increase in the predictor; approximate percentage changes in CV can be estimated us-

Table 4. Multivariate linear regression analysis of factors associated with the MODD.

Variable	β coefficient	SE	*t*-value	*p*-value	95% CI (lower)	95% CI (upper)
Age	0.027	0.005	5.761	<0.001	0.018	0.036
Gender	0.024	0.076	0.318	0.751	–0.126	0.175
BMI	–0.036	0.008	–4.248	<0.001	–0.053	–0.019
NYHA class III	–0.076	0.076	–0.998	0.320	–0.225	0.074
NYHA class IV	–0.023	0.094	–0.245	0.807	–0.209	0.163
Diabetes duration	0.029	0.006	4.929	<0.001	0.018	0.041
Hypertension	–0.016	0.083	–0.189	0.850	–0.180	0.148
eGFR	–0.002	0.002	–1.378	0.170	–0.005	0.001
Log(NT-proBNP)	0.090	0.034	2.648	0.009	0.023	0.158
Family history of diabetes	0.175	0.069	2.536	0.012	0.039	0.312
Cardiovascular disease history	0.016	0.073	0.212	0.832	–0.129	0.160
HbA1c	0.125	0.025	5.070	<0.001	0.076	0.174
C-peptide	–0.176	0.048	–3.690	<0.001	–0.270	–0.082

Note: BMI, body mass index; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, glycated hemoglobin; CI, confidence interval.

Table 5. Multivariate linear regression analysis of factors associated with MAGE.

Variable	β coefficient	SE	*t*-value	*p*-value	95% CI (lower)	95% CI (upper)
Age	0.015	0.007	1.976	0.050	0.000	0.029
Gender	–0.130	0.120	–1.084	0.280	–0.369	0.108
BMI	0.037	0.013	2.746	0.007	0.010	0.063
NYHA class III	0.025	0.120	0.207	0.837	–0.212	0.261
NYHA class IV	0.211	0.149	1.423	0.157	–0.082	0.505
Diabetes duration	0.002	0.009	0.217	0.829	–0.017	0.021
Hypertension	0.200	0.131	1.526	0.129	–0.059	0.460
eGFR	–0.001	0.003	–0.503	0.616	–0.006	0.004
Log(NT-proBNP)	0.162	0.054	2.997	0.003	0.055	0.268
Family history of diabetes	0.204	0.109	1.864	0.065	–0.012	0.420
Cardiovascular disease history	0.265	0.116	2.288	0.024	0.036	0.494
HbA1c	0.196	0.039	5.032	<0.001	0.119	0.273
C-peptide	–0.284	0.075	–3.772	<0.001	–0.433	–0.135

Note: BMI, body mass index; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, glycated hemoglobin; CI, confidence interval.

ing the formula $(e^{\beta} - 1) \times 100\%$. Model performance was evaluated using the adjusted coefficient of determination R^2. All statistical tests were two-sided, and a p-value $<$ 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

As shown in Table 1, the mean age of the 150 patients was 67.81 $\pm$ 7.6 years, and 106 patients (70.7%) were male. The mean duration of diabetes was 11.87 $\pm$ 5.73 years, and the mean HbA1c level was 8.47 $\pm$ 1.40%. In terms of cardiac function, the majority of patients (80.0%) were classified as NYHA functional class II–III. The mean eGFR was 66.03 $\pm$ 21.23 mL/min/1.73 m^2. The GV indices were as follows: SDBG, 1.51 $\pm$ 0.44 mmol/L; CV, 18.69 $\pm$ 4.53%; MODD, 1.78 $\pm$ 0.56 mmol/L; and MAGE, 4.05 $\pm$ 0.79 mmol/L.

3.2 Multivariate Regression Analysis Results

3.2.1 Factors Associated With SDBG

Multiple linear regression analysis demonstrated that age (β = 0.020, $p < 0.001$), diabetes duration (β = 0.028, $p < 0.001$), log(NT-proBNP) (β = 0.085, p = 0.002), family history of diabetes (β = 0.184, p = 0.001), and HbA1c (β = 0.062, p = 0.002) were positively associated with SDBG, while C-peptide level was negatively associated with SDBG (β = –0.219, $p < 0.001$). This model explained 49.6% of the variance in SDBG (adjusted R^2 = 0.496; Table 2).

3.2.2 Factors Associated With CV

Independent factors associated with log-transformed CV included age (β = 0.009, $p < 0.001$), diabetes duration (β = 0.011, $p < 0.001$), log(NT-proBNP) (β = 0.046, p = 0.002), family history of diabetes (β = 0.088, p = 0.004),

and C-peptide level (β = –0.080, $p < 0.001$). The adjusted R^2 of this model was 0.350, indicating that 35% of the variance in log(CV) was explained (Table 3).

For the log-transformed CV model, regression coefficients represent the change in log(CV) per unit increase in the predictor. The approximate percentage change in CV can be calculated as $(e^{\beta} - 1) \times 100\%$. For example, the coefficient for diabetes duration ($\beta = 0.011$) corresponds to an approximate 1.1% increase in CV for each additional year of diabetes duration.

3.2.3 Factors Associated With MODD

MODD was positively associated with age ($\beta = 0.027$, $p < 0.001$), diabetes duration ($\beta = 0.029$, $p < 0.001$), log(NT-proBNP) ($\beta = 0.090$, $p = 0.009$), family history of diabetes ($\beta = 0.175$, $p = 0.012$), and HbA1c ($\beta = 0.125$, $p < 0.001$). In contrast, MODD was negatively associated with BMI (β = –0.036, $p < 0.001$) and C-peptide (β = –0.176, $p < 0.001$). The model explained 49.1% of the variance in MODD (adjusted $R^2 = 0.491$; Table 4).

3.2.4 Factors Associated With MAGE

The primary factors associated with MAGE included BMI ($\beta = 0.037$, $p = 0.007$), log(NT-proBNP) ($\beta = 0.162$, $p = 0.003$), history of cardiovascular disease ($\beta = 0.265$, $p = 0.024$), HbA1c ($\beta = 0.196$, $p < 0.001$), and C-peptide level (β = –0.284, $p < 0.001$). In contrast to other GV indices, diabetes duration was not significantly associated with MAGE ($\beta = 0.002$, $p = 0.829$), while the association with age was of borderline statistical significance ($\beta = 0.015$, $p = 0.050$). This model explained 34.9% of the variance in MAGE (adjusted $R^2 = 0.349$; Table 5).

4. Discussion

This study systematically examined independent factors influencing four GV indices in hospitalized patients with T2DM and HF using multiple linear regression analysis. The results demonstrate that, although significant overlaps exist among the factors associated with different GV metrics, each index also exhibits distinct determinants, reflecting its unique physiological dimensions. These findings enhance current understanding of the complexity of glycemic regulation in this high-risk population and provide a basis for individualized glycemic management strategies.

First, C-peptide level demonstrated a consistent and significant negative association with all four GV indices. This finding strongly supports the central role of endogenous insulin secretory capacity in maintaining glucose homeostasis in patients with T2DM and HF. Preserved β-cell function allows for timely and adequate insulin secretion in response to dynamic glucose changes, effectively buffering against glycemic fluctuations induced by various stressors, including neurohormonal activation associated with HF [21]. Within the bidirectional pathophysiological interaction between T2DM and HF, both conditions may accelerate β-cell dysfunction by exacerbating insulin resistance and chronic low-grade inflammation [1]. Consequently, preservation of residual β-cell function should represent a cornerstone of glycemic management in this patient population.

However, interpretation of C-peptide levels is complex, as they are influenced not only by β-cell function but also by the degree of insulin resistance. Insulin resistance may lead to compensatory hyperinsulinemia and elevated fasting C-peptide levels [22]. The strong negative associations observed in the present study suggest that, in this specific clinical context, the β-cell functional component of C-peptide may predominate as a determinant of GV. This finding underscores the critical relevance of preserved insulin secretory capacity for maintaining glycemic stability, even in the presence of concomitant insulin resistance.

Second, age emerged as another consistently relevant factor, showing significant positive associations with SDBG, log(CV), and MODD (all $p < 0.001$), although it did not reach statistical significance in the MAGE model ($p = 0.050$). These findings suggest a progressive decline in glycemic stability with advancing age, potentially attributable to age-related reductions in muscle mass leading to worsening insulin resistance, diminished β-cell responsiveness, and impaired autonomic nervous system function [23]. Collectively, these mechanisms may predispose older individuals to greater fluctuations in glucose levels. Accordingly, glycemic management in elderly patients with T2DM and HF may require a more cautious and individualized approach, potentially involving less stringent glycemic targets and the preferential use of therapies with a low risk of hypoglycemia to minimize the adverse consequences associated with excessive glycemic fluctuations [24].

This study further revealed that different GV indices have distinct determinants, reflecting their unique physiological interpretations of glucose fluctuations, with important implications for clinical practice. SDBG, which was predominantly influenced by age, diabetes duration, HF severity (as reflected by NT-proBNP), and β-cell function, underscores the close relationship between the magnitude of absolute glycemic fluctuation and chronic disease progression, cardiac status, and intrinsic insulin secretory capacity.

Variable transformation for CV was performed based on formal residual normality testing (Shapiro-Wilk $p < 0.001$ for untransformed vs. $p = 0.223$ after logarithmic transformation), thereby ensuring that model assumptions were satisfied and enhancing the reliability of statistical inference. In contrast, MODD, SDBG, and MAGE were analyzed without transformation because their residuals met normality assumptions. This methodological approach ensured that the assumptions underlying regression analysis were adequately met, thereby increasing the robustness of the results. Notably, regression coefficients derived from transformed models must be interpreted on their respective

mathematical scales, which may introduce additional complexity but allows for more accurate estimation of effect sizes in clinical interpretations.

Notably, HbA1c was not an independent factor for log(CV) in the multivariate model. Because CV is calculated as SDBG divided by mean glucose, it inherently adjusts for differences in average glycemia and is therefore considered the gold standard for measuring "relative variability" [10]. Our findings indicate that long-term glycemic control, as reflected by HbA1c, and relative glucose fluctuation, as reflected by CV, represent largely independent dimensions [25]. This dissociation may explain why some patients achieve HbA1c targets yet continue to experience marked GV and remain at elevated risk for complications [26].

Furthermore, CV was primarily associated with HF severity, as indicated by NT-proBNP levels, highlighting the direct influence of cardiac dysfunction on glycemic stability. One plausible mechanism involves impaired tissue glucose delivery and altered glucose utilization efficiency secondary to reduced cardiac output. While recent studies have suggested potential links between HF severity, metabolic regulators such as adropin, and insulin sensitivity [27–29], these mechanisms were not directly examined in the present cohort. Therefore, the observed association between NT-proBNP and GV warrants further investigation to elucidate the underlying pathophysiological pathways.

The divergent associations observed between BMI and different GV indices warrant particular attention. BMI demonstrated a significant negative association with MODD but a positive association with MAGE. This apparent paradox may be explained by distinct physiological mechanisms. Higher BMI may confer greater day-to-day glycemic stability through nutritional reserves and metabolic inertia [30], potentially accounting for the negative association with MODD. In contrast, obesity-related insulin resistance may predispose individuals to larger acute glucose excursions in response to prandial stimuli [31], aligning with the positive association observed with MAGE. These findings align with the so-called "obesity paradox" described in chronic conditions such as HF and underscore the complexity of metabolic regulation in this population [32].

Importantly, sharp glucose fluctuations have been shown to exert acute and severe adverse effects on the vascular system by inducing oxidative stress, exacerbating endothelial dysfunction, and promoting an inflammatory response [33]. These pathophysiological effects align more closely with the glucose "peaks and troughs" captured by MAGE, reinforcing the clinical relevance of index-specific interpretation when assessing GV in patients with concomitant T2DM and HF.

The clinical implications of the present study suggest that glycemic management in patients with T2DM and HF may benefit from a multidimensional assessment approach. For instance, in patients with impaired cardiac function, as indicated by elevated NT-proBNP levels, consideration may be given to cardioprotective therapies known to improve glycemic stability, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors [34], with attention to CV values [9]. Similarly, in patients with an extensive history of cardiovascular disease, therapeutic strategies targeting reductions in MAGE may be warranted. However, these clinical suggestions should be viewed as preliminary and require validation in prospective, adequately powered interventional studies.

A noteworthy finding in the study was the presence of elevated mean HbA1c levels, accompanied by relatively low SDBG values. We hypothesize that this finding may be attributable to the standardized inpatient environment, which minimizes lifestyle-related glucose triggers, and the use of intermittent capillary blood glucose monitoring. Compared with continuous glucose monitoring (CGM), intermittent capillary measurements may underestimate the true amplitude and frequency of acute glycemic excursions. Consequently, the GV indices reported in this study should be interpreted as reflecting glycemic stability under controlled hospitalized conditions rather than glycemic patterns in free-living ambulatory settings.

Several important limitations of this study should be acknowledged. First, the single-center and retrospective design introduces an inherent risk of selection bias and limits the generalizability of the findings. Additionally, the reliance on electronic medical records precluded systematic collection of several potentially relevant confounding factors, including detailed glucose-lowering management regimens (e.g., specific insulin protocols and use of SGLT2 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists), dietary intake, and physical activity levels. Consequently, the observational and cross-sectional nature of the analysis precludes causal inference regarding the relationships between identified factors and GV outcomes.

Additionally, although the sample size of 150 patients was sufficient for exploratory analyses, it remains relatively modest for multivariable linear regression models with multiple predictors, potentially affecting model stability and the precision of estimates. Glycemic variability was assessed using capillary blood glucose measurements rather than CGM, which is considered the gold standard for evaluating GV, especially for indices such as MAGE [35]. Although the standardized seven-point capillary glucose monitoring protocol employed in this study represents a pragmatic and widely applicable approach in the inpatient setting, it likely underestimates the true magnitude of acute glucose fluctuations. Future studies incorporating CGM technology and larger, multicenter cohorts will be essential to validate and extend these findings.

5. Conclusion

Glycemic variability in hospitalized patients with T2DM and HF is influenced by multiple clinical factors, with C-peptide level, age, diabetes duration, HF severity (as reflected by NT-proBNP), and overall glycemic control representing the primary influencing factors. Different GV indices exhibit unique spectra of associated factors, reflecting the diverse dimensions of glycemic variability they represent. Accordingly, clinical practice may potentially benefit from a multidimensional assessment of GV. For example, greater attention to CV may be particularly relevant in patients with elevated NT-proBNP levels, while strategies aimed at reducing MAGE may be considered in patients with a history of cardiovascular disease. However, these implications should be interpreted with caution, as they are derived from an exploratory analysis, and their clinical utility requires validation in prospective intervention studies.

Key Points

• C-peptide levels demonstrated a significant negative association with all indices of glycemic variability, underscoring that preserved β-cell function is critical for maintaining glucose homeostasis in patients with T2DM and HF, and should be a central consideration in clinical management.

• N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of HF severity, was an independent positive predictor of most GV indices, revealing that cardiac dysfunction itself constitutes a clinically measurable and relevant pathophysiological driver of dysglycemia.

• The finding that BMI was negatively associated with MODD but positively associated with MAGE highlights that glycemic variability is a multidimensional concept, with distinct components, such as day-to-day stability and acute glucose excursions, being influenced by distinct physiological mechanisms.

• Taken together, these findings suggest that glycemic management in patients with T2DM and HF should extend beyond exclusive reliance on HbA1c and incorporate a multidimensional assessment of GV to support more individualized therapeutic strategies, such as prioritizing CV in patients with advanced HF and targeting MAGE reduction in those with established cardiovascular disease.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

YJ and JBM designed the research study. YJ performed the research. JBM analyzed the data. YJ and JBM drafted this article. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of People's Hospital of Baishan (approval number: KY2025023). All procedures followed the ethical principles outlined in the Declaration of Helsinki. Informed consent was waived by the Ethics Committee of People's Hospital of Baishan due to the retrospective study design and the anonymization of all patient data.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, *et al*. Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America. Journal of Cardiac Failure. 2019; 25: 584–619. https://doi.org/10.1016/j.cardfail.2019.05.007.

[2] Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, *et al*. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure. 2018; 20: 853–872. https://doi.org/10.1002/ejhf.1170.

[3] Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, *et al*. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC. Heart Failure. 2015; 3: 136–145. https://doi.org/10.1016/j.jchf.2014.08.004.

[4] Sun B, Luo Z, Zhou J. Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. Cardiovascular Diabetology. 2021; 20: 9. https://doi.org/10.1186/s12933-020-01200-7.

[5] Cardoso CRL, Leite NC, Moram CBM, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. Cardiovascular Diabetology. 2018; 17: 33. https://doi.org/10.1186/s12933-018-0677-0.

[6] Paolillo S, Marsico F, Prastaro M, Renga F, Esposito L, De Martino F, *et al*. Diabetic Cardiomyopathy: Definition, Diagnosis, and Therapeutic Implications. Heart Failure Clinics. 2019; 15: 341–347. https://doi.org/10.1016/j.hfc.2019.02.003.

[7] Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, *et al*. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes. 2008; 57: 1349–1354. https://doi.org/10.2337/db08-0063.

[8] McMurray JJV, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. The Lancet. Diabetes & Endocrinology. 2014; 2: 843–851. https://doi.org/10.1016/S2213-8587(14)70031-2.

[9] Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, *et al*. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019; 42: 1593–1603. https://doi.org/10.2337/dci19-0028.

[10] Rodbard D. Glucose Variability: A Review of Clinical Applications and Research Developments. Diabetes Technology & Therapeutics. 2018; 20: S25–S215. https://doi.org/10.1089/dia.2018.0092.

[11] American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45: S83–S96. https://doi.org/10.2337/dc22-S006.

[12] American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. Diabetes Care. 2024; 47: S20–S42. https://doi.org/10.2337/dc24-S002.

[13] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726. https://doi.org/10.1093/eurheartj/ehab368.

[14] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895–e1032. https://doi.org/10.1161/CIR.0000000000001063.

[15] Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, *et al*. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. European Journal of Heart Failure. 2019; 21: 715–731. https://doi.org/10.1002/ejhf.1494.

[16] DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes. 2013; 62: 1405–1408. https://doi.org/10.2337/db12-1610.

[17] Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, *et al*. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocrine Practice. 2011; 17: 1–53. https://doi.org/10.4158/ep.17.s2.1.

[18] Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2020 executive summary. Endocrine Practice. 2020; 26: 107–139. https://doi.org/10.4158/CS-2019-0472.

[19] Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. Diabetologia. 1972; 8: 342–348. https://doi.org/10.1007/BF01218495.

[20] Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2016. Available at: http://www.R-project.org/ (Accessed: 15 March 2022).

[21] Melenovsky V, Benes J, Franekova J, Kovar J, Borlaug BA, Segetova M, *et al*. Glucose Homeostasis, Pancreatic Endocrine Function, and Outcomes in Advanced Heart Failure. Journal of the American Heart Association. 2017; 6: e005290. https://doi.org/10.1161/JAHA.116.005290.

[22] Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, *et al*. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA. 2017; 317: 2515–2523. https://doi.org/10.1001/jama.2017.7596.

[23] Xiang Q, Li Y, Lip GYH, Cuthbertson DJ, Huang W, Zhong Z, *et al*. Joint trajectories of skeletal muscle and fat mass in relation to glucose homeostasis: 6-Year findings from adults aged ≥50 years. Diabetes, Obesity & Metabolism. 2025; 27: 7133–7145. https://doi.org/10.1111/dom.70113.

[24] LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, *et al*. Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism. 2019; 104: 1520–1574. https://doi.org/10.1210/jc.2019-00198.

[25] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. The Lancet. Diabetes & Endocrinology. 2019; 7: 221–230. https://doi.org/10.1016/S2213-8587(18)30136-0.

[26] Ceriello A, Rizvi AA, Rizzo M. Glycemic Variability, Glycated Hemoglobin, and Cardiovascular Complications: Still a Dilemma in Clinical Practice. Advances in Therapy. 2022; 39: 1–4. https://doi.org/10.1007/s12325-021-01942-0.

[27] Berezin AA, Obradovic Z, Fushtey IM, Berezina TA, Novikov EV, Schmidbauer L, *et al*. The Impact of SGLT2 Inhibitor Dapagliflozin on Adropin Serum Levels in Men and Women with Type 2 Diabetes Mellitus and Chronic Heart Failure. Biomedicines. 2023; 11: 457. https://doi.org/10.3390/biomedicines11020457.

[28] Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, *et al*. Adropin is a novel regulator of endothelial function. Circulation. 2010; 122: S185–S192. https://doi.org/10.1161/CIRCULATIONAHA.109.931782.

[29] Butler AA, Tam CS, Stanhope KL, Wolfe BM, Ali MR, O'Keeffe M, *et al*. Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. The Journal of Clinical Endocrinology and Metabolism. 2012; 97: 3783–3791. https://doi.org/10.1210/jc.2012-2194.

[30] Alebna PL, Mehta A, Yehya A, daSilva-deAbreu A, Lavie CJ, Carbone S. Update on obesity, the obesity paradox, and obesity management in heart failure. Progress in Cardiovascular Diseases. 2024; 82: 34–42. https://doi.org/10.1016/j.pcad.2024.01.003.

[31] Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? Journal of Diabetes Science and Technology. 2008; 2: 1094–1100. https://doi.org/10.1177/193229680800200618.

[32] Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? Vascular Health and Risk Management. 2019; 15: 89–100. https://doi.org/10.2147/VHRM.S168946.

[33] Su G, Mi S, Tao H, Li Z, Yang H, Zheng H, *et al*. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovascular Diabetology. 2011; 10: 19. https://doi.org/10.1186/1475-2840-10-19.

[34] Sarafidis PA, Tsapas A. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine. 2016; 374: 1092. https://doi.org/10.1056/NEJMc1600827.

[35] Monnier L, Colette C, Boegner C, Pham TC, Lapinski H, Boniface H. Continuous glucose monitoring in patients with type 2 diabetes: Why? When? Whom? Diabetes & Metabolism. 2007; 33: 247–252. https://doi.org/10.1016/j.diabet.2006.11.007.