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A CGM-Based model for predicting hypoglycemia in type 2 diabetes patients with TIR in target

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Abstract

Aim This study aims to predict risk factors for hypoglycemia in patients with type 2 diabetes mellitus (T2DM) using continuous glucose monitoring (CGM) and with time in range (TIR) > 70%.

Methods Data from 111 patients with T2DM who underwent CGM with TIR > 70% were analyzed. A hypoglycemia episode was defined as CGM-detected glucose < 3.9mmol/L sustained for at least 5 min. Logistic regression analysis was performed to examine the relationship between hypoglycemia and mean blood glucose (MBG), glycemic variability (GV) metrics [including mean amplitude of glucose excursion (MAGE), largest amplitude of glycemic excursion (LAGE), mean of daily difference (MODD), coefficient of variation (CV), standard deviation (SD)], and low blood glucose index (LBGI). A nomogram model was constructed, and its diagnostic performance was assessed. Data were bootstrapped 1000 times for internal validation, and a calibration curve was drawn to evaluate the model's predictive ability. Decision curve analysis was performed to assess its clinical usefulness.

Results Among the 111 included patients, 53 experienced hypoglycemic event during wearing CGM (47.75%). GV metrics were higher in hypoglycemia group, while MBG was lower. The multivariable logistic regression analysis showed that the MBG, GV metrics, LBGI were independently associated with hypoglycemia. The receiver operating characteristics (ROC) analysis indicated that the area under the curve (AUC) for the MBG-SD-LBGI model was 0.93 (95% CI = 0.88–0.97). The calibration curve showed good consistency between the predicted and observed probabilities. Decision curve analysis demonstrated strong clinical applicability.

Conclusion This study demonstrates a significant correlation between CGM metrics and hypoglycemia in patients with T2DM who achieved TIR > 70%. These findings suggest that CGM metrics can predict the risk of hypoglycemia in

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T2DM patients with a TIR > 70%, and the nomogram developed from these metrics holds strong potential for clinical application.

Keywords Hypoglycemia, Type 2 diabetes, Continuous glucose monitoring, Time in range, Nomogram

Introduction

It has been widely acknowledged that stringent glycemic control can reduce the risk of both microvascular and macrovascular complications in patients with diabetes [1, 2]. However, achieving tight glycemic control may also increase the risk of hypoglycemia [3, 4]. Severe hypoglycemia is associated with increased risk of all-cause mortality and transient ischemic attacks in patients with type 2 diabetes mellitus (T2DM) [5]. Furthermore, patients who experienced hypoglycemia episodes often report a diminished health-related quality of life and incur higher healthcare expenditures [6]. Hypoglycemia also limits the efficacy of insulin therapy and significantly impacts patient morbidity and mortality [7, 8]. Therefore, preventing hypoglycemia is crucial, especially for patients aiming for strict glycemic control.

Glycosylated hemoglobin (HbA1c) is the standard measure for assessing long-term glycemic control in individuals with diabetes. However, HbA1c has several limitations. It lacks information about acute glycemic fluctuations, such as hypo- or hyperglycemia, and fails to quantify the magnitude and frequency of both intraday and interday glycemic variability (GV) [9, 10]. Additionally, HbA1c levels are affected by various factors, including renal failure, hemoglobinopathies, and chronic liver disease [11, 12]. In recent years, continuous glucose monitoring (CGM) has emerged as a superior method for providing a more comprehensive assessment of glycemic patterns and minimizing the risk of hypoglycemia. Since 2020, Time in range (TIR) has been recommended as a key metric for assessing glycemic management, representing the percentage of time during which an individual's blood glucose remains within a target range of 3.9–10 mmol/L [13, 14]. Achieving a TIR > 70% is generally recommended for most adults with diabetes, which roughly corresponds to an HbA1c of approximately 7% [15].

Previous studies have demonstrated that low blood glucose index (LBGI) is an independent risk factor for hypoglycemia in patients with T2DM who maintain good glycemic control (HbA1c < 7%) [16]. A previous study proposed a three-dimensional scoring model integrating percentage GV, LBGI, and high blood glucose index (HBGI) to identify both the most alarming dimension of glycemia and the individuals with Type 1 Diabetes mellitus (T1DM) in most urgent need of assistance [17]. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia was validated in T1DM populations with average TIR of 59.9% to assist with basic clinical interpretation of CGM data [18]. An explainable machine learning approach based on CGM metrics was used to assess the risk of hypoglycemia in hemodialysis patients [19]. However, despite the increasing use of CGM, the incidence of hypoglycemia in adults with T2DM with TIR > 70% remains poorly understood. Therefore, the role of CGM-derived metrics in identifying the risk of hypoglycemia in this population requires further investigation.

In this study, we examined a well-characterized cohort of adults with T2DM who achieved a TIR > 70%. We aimed to explore the relationship between CGM-derived metrics and the risk of hypoglycemia. By utilizing CGM-derived metrics data to identify high-risk groups for hypoglycemia, we hope to provide clinical insights into the incidence of hypoglycemia in this population, ultimately contributing to personalized diabetes treatment and improving overall diabetes management.

Methods

Study population

This retrospective, single-center study was conducted at the Department of Endocrinology and Metabolic Disease, the Third Affiliated Hospital of Sun Yat-sen University. Data were collected between January 2018 and October 2019. T2DM was diagnosed based on the 1999 World Health Organization (WHO) criteria. Inclusion criteria were aged ≥ 18 years, diagnosed with T2DM, a stable antihyperglycemic regimen over the previous three months, and a TIR > 70% according to CGM (iPro^{TM}2, Medtronic MiniMed, Inc.) data. Exclusion criteria included diabetic ketoacidosis, hyperglycemic hyperosmolar state, stress conditions, severe kidney or liver insufficiency, pregnancy, other conditions affecting glucose metabolism, or CGM data duration of less than seven days. The inclusion process is illustrated in Fig. 1. Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (IRB No. [2020] 02-107-01).

Measurements

Demographic and clinical data, including diabetes management, were collected. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest, while hip circumference was measured as maximum circumference over the greater trochanter. The waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2). After a 10-h overnight fast, fasting blood

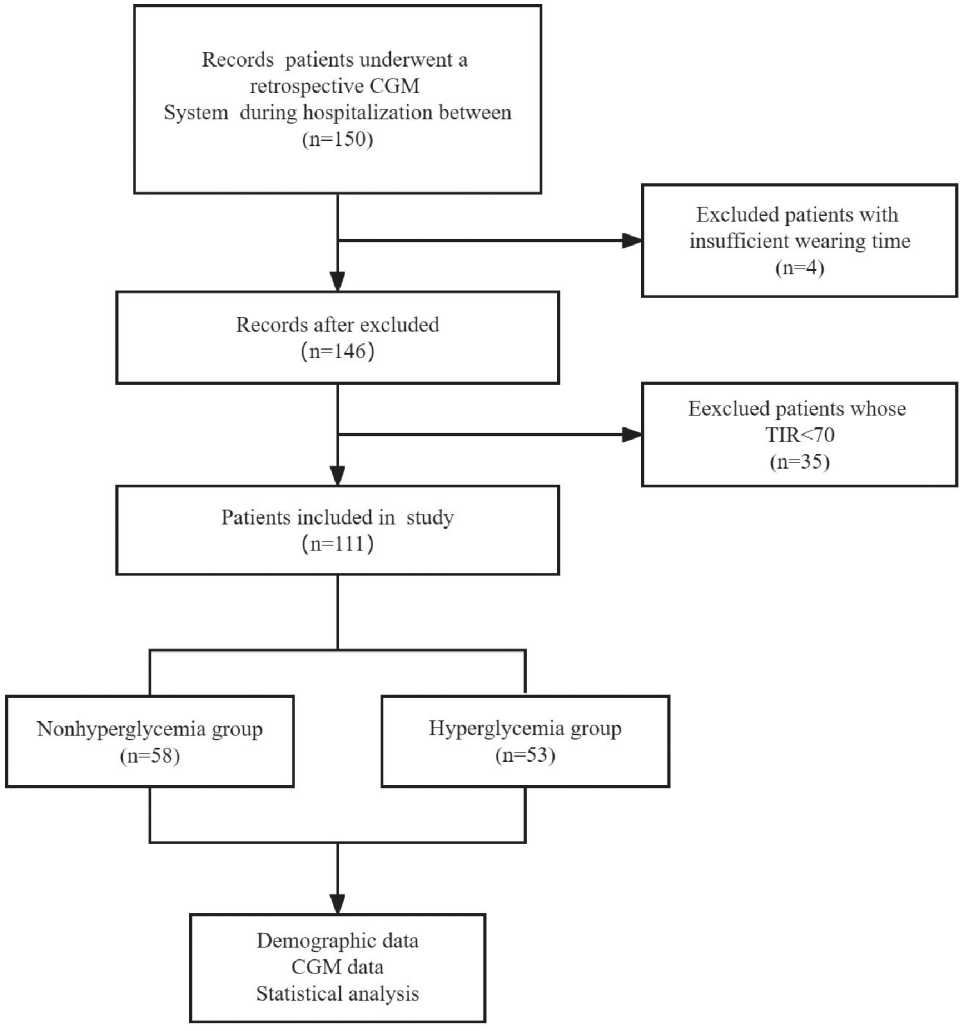

Fig. 1 Flow chart of patients' inclusion process

samples were collected for measurements of HbA1c, lipid profiles, liver enzymes, and creatinine. Fasting, 0.5-hour, and 2-hour postprandial serum C-peptide levels were measured during a mixed-meal test. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration International Equations based on serum creatinine ($CKD\text{-}EPI_{SCr}$) [20].

CGM metrics

Each participant underwent seven days of retrospective CGM using the iPro^{TM}2 system (Medtronic MiniMed, Inc), with the data blinded to patients and physicians. During the CGM-wearing period, participants followed a standard diet providing 50% caloric content as carbohydrates, 20–25% fat, and 15-20% proteins, with a total calorie intake of 25–30 kcal/kg per day. Capillary blood glucose was measured at least 4 times per day using One-Touch Ultra (Life Scan Inc., Milpitas, CA) to calibrate the CGM system. CGM data were downloaded using CareLink iPro software (Minimed, Medtronic, Inc), with the first 12 h excluded due to potential system instability [21].

An episode of hypoglycemia on CGM was defined as a sensor glucose level < 3.9mmol/L for at least 5 min [22]. TIR was defined as the percentage of time glucose levels were between 3.9 mmol/L and 10.0 mmol/L (3.9–10.0 mmol/L [inclusive]). GV was assessed using mean amplitude of glycemic excursions (MAGE), the largest amplitude of glycemic excursion (LAGE), the mean of daily differences (MODD), coefficient of variation (CV), and standard deviation (SD) [23]. The glycemic risk index calculated in this study was LBGI [23].

Screening of relevant variables and development of nomogram

Univariate logistic regression analysis was performed to identify significant CGM-derived, clinical, and laboratory

indicators associated with hypoglycemia. Multivariate logistic regression was further uesd to evaluate CGM metrics (e.g., MBG, GV metrics, and LBGI) and confounding factors. A nomogram was constructed based on the independent predictors identified in multivariate analysis to estimate hypoglycemia risk in T2DM patients with a TIR > 70%.

Statistical analysis

Data were presented as mean ± SD for continuous variables, and n (%) for categorical variables. Student's t-test was used to compare normally distributed continuous variables between groups, while the Mann–Whitney U test was applied to skewed data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was employed to identify the key indicators associated with hypoglycemia. The nomogram's performance was assessed by calculating the area under the curve (AUC), sensitivity, specificity, accuracy, and predictive values. Internal validation was conducted using 1000 bootstrap samples to minimize overfitting bias. Calibration was verified using the Hosmer-Lemeshow test and a calibration curve. Decision curve analysis (DCA) quantified the model's clinical utility. Statistical analyses were performed using SPSS software version 23.0 (IBM, Armonk, New York, United States) and R version 4.4.1 (http://www.r-project.org). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Clinical characteristics of study participants

Table 1 summarized the clinical characteristics of the 111 participants with TIR > 70%. The participants had a mean age of 56.87 ± 11.80 years, a mean diabetes duration of 8.17 ± 6.09 years, and an average HbA1c level of 6.75 ± 1.26%. Hypoglycemia was observed in 53 patients (47.75%), with 21 patients (18.92%) experiencing level 2 hypoglycemia (Time below range [TBR] < 3.0mmol/L). No significant differences were found in age, HbA1c levels, diabetes complications, or fasting glucose levels between the hypoglycemia and non-hypoglycemia groups. However, the hypoglycemic group had a significantly higher proportion of participants treated with premixed insulin compared to the non-hypoglycemia group (11.32% vs. 1.72%, $p = 0.044$).

Table 1 Clinical characteristics of study participants

Variables	All (n = *111*)	Nonhypoglycemia (n = *58*)	Hypoglycemia (n = *53*)	*p*
Age, years	56.87 ± 11.80	56.83 ± 11.90	56.92 ± 11.80	0.97
Sex, male/female, n	58/53	30/28	30/23	0.61
Duration of diabetes, years	8.17 ± 6.09	8.34 ± 6.41	7.99 ± 5.77	0.77
BMI, kg/m^2	24.73 ± 3.59	24.87 ± 4.09	24.58 ± 2.98	0.67
HbA1c, %	6.75 ± 1.26	6.88 ± 1.40	6.61 ± 1.07	0.27
eGFR, mL/mi/1.73 m^2	93.33 ± 19.62	92.82 ± 20.10	93.90 ± 19.26	0.78
Fasting glucose, mmol/l	6.54 ± 1.42	6.90 ± 1.42	6.55 ± 1.41	0.26
Diabetes complications, n (%)	16(14.41)	10(17.24)	6(11.32)	0.38
	16(14.41)	9(15.52)	7(13.20)	0.73
Nephropathy	31(27.93)	20(34.48)	11(20.75)	0.11
Retinopathy	65(58.59)	37(63.79)	28(52.83)	0.24
Neuropathy				
Macroangiopathy				
Oral hypoglycemic agents, n (%)				
Sulfonylurea	26(23.42)	8(13.79)	14 (26.41)	0.096
α-Glucosidase	34(30.63)	16(27.59)	18(33.96)	0.47
inhibitor	65(58.56)	34(58.62)	31(58.49)	0.99
Metformin	30(27.02)	12(20.69)	18(33.96)	0.12
DPP4 inhibitor	3(2.70)	1(1.72)	2(3.77)	0.61
GLP-1 receptor	2(1.80)	2(3.45)	0(0)	-
agonists	8(7.21)	5(8.62)	3(5.66)	0.72
Thiazolidinedione	28(25.23)	15(25.86)	13(24.52)	0.87
SGLT2 inhibitor	4(3.60)	4(6.90)	0(0)	0.071
Insulin, n (%)	14(12.61)	8(13.79)	6(11.32)	0.46
Only Basal insulin	3(2.70)	2(3.45)	1(1.89)	0.53
Only Bolus insulin	7(6.31)	1(1.72)	6(11.32)	0.044
Basal + bolus inulin				
Premixed insulin				
CGM metrics				
TIR (3.9-10.0mmol/L)	88.98 ± 11.23	90.30 ± 13.54	87.57 ± 7.93	0.20
[a],%	2.51 ± 4.16	-	5.26 ± 4.68	-
TBR (< 3.9mmol/L) [a], %	0.57 ± 1.67	-	1.19 ± 2.27	-
TBR (< 3.0mmol/L)[a], %				
MBG[a], mmol/L	7.16 ± 0.87	7.38 ± 0.94	6.91 ± 0.71	0.004
CV[a], %	22.23 ± 7.86	18.29 ± 6.10	26.64 ± 7.29	< 0.001
MODD[a], mmol/L	1.42 ± 0.55	1.27 ± 0.55	1.59 ± 0.50	0.002
MAGE[a], mmol/L	3.78 ± 1.62	3.27 ± 1.47	4.34 ± 1.60	< 0.001
LAGE[a], mmol/L	8.41 ± 2.93	7.09 ± 2.49	9.89 ± 2.68	< 0.001

CGM-derived metrics

Participants in the hypoglycemia group exhibited significantly higher levels of MAGE (4.34 ± 1.60 vs. 3.27 ± 1.47 mmol/L, $p < 0.001$), LAGE (9.89 ± 2.68 vs. 7.09 ± 2.49 mmol/L, $p < 0.001$), MODD (1.59 ± 0.50 vs. 1.27 ± 0.55 mmol/L, $p = 0.002$), CV (26.64 ± 7.29 vs. 18.29 ± 6.10%, $p < 0.001$), SD (1.94 ± 0.51 vs. 1.36 ± 0.55 mmol/L,

Table 1 (continued)

Variables	All (n = *111*)	Nonhypoglycemia (n = *58*)	Hypoglycemia (n = *53*)	*p*
SD[a], mmol/L	1.64 ± 0.60	1.36 ± 0.55	1.94 ± 0.51	< 0.001
LBGI[a]	1.61 ± 1.57	0.72 ± 0.82	2.60 ± 1.62	< 0.001

Data are mean ± SD or *n* (%)

CV, coefficient of variation; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; LAGE, largest amplitude of glycemic excursion; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MBG, mean blood glucose; MODD, mean of daily difference; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2; TBR, Time below range; TIR, Time in range

[a]Measured by the continuous glucose monitoring system

$p < 0.001$) and LBGI (2.60 ± 1.62 vs. 0.72 ± 0.82, $p < 0.001$), and lower level of MBG (6.91 ± 0.71 vs. 7.38 ± 0.94 mmol/L, $p = 0.004$) (Table 1). Hypoglycemia occurred more frequently during nighttime (22:00–6:00) compared to the divided daytime periods (6:00–12:00,12:00–18:00,18:00–22:00) (40.47% vs.18.75% vs.16.71% vs.15.54%, $p < 0.001$). The mean percentage of the TBR (< 3.9 mmol/L) and TBR (< 3.0 mmol/L) was 5.26 ± 4.68% and 1.19 ± 2.27% in the hypoglycemia group, respectively.

Logistic regression analyses

The univariate analysis identified several significant risk factors for hypoglycemia, including diabetic peripheral neuropathy (DPN) (OR = 2.33, 95% CI: 1.03–5.26, $p = 0.041$), insulin use (OR = 1.06, 95%CI: 0.46–2.46, $p = 0.89$), MBG (OR = 0.51, 95%CI: 0.32–0.83, $p = 0.006$), CV (OR = 1.20, 95%CI: 1.12–1.30, $p < 0.001$), MODD (OR = 3.35, 95%CI: 1.49–7.57, $p = 0.004$), MAGE (OR = 1.73, 95%CI: 1.31–2.28, $p < 0.001$), LAGE (OR = 1.52, 95%CI: 1.27–1.82, $p < 0.001$), SD (OR = 7.50, 95%CI: 3.16–17.82, $p < 0.001$) and LBGI (OR = 5.46, 95%CI: 2.76–10.78, $p < 0.001$) were significantly associated with hypoglycemia (Table 2).

Table 2 Clinical markers of hypoglycemia analyzed by univariate logistic regression

Model	Dependent variable	OR (95%CI)	*P*
Univariate model	Age, years	1.00 (0.97 ~ 1.03)	0.97
	Duration of diabetes, years	1.00 (1.00 ~ 1.00)	0.76
	eGFR	1.00 (0.98 ~ 1.02)	0.86
	Oral hypoglycemia agent	0.50 (0.16 ~ 1.57)	0.24
	Insulin	1.06 (0.46 ~ 2.46)	0.89
	Diabetes complications		
	Nephropathy	1.63 (0.55 ~ 4.85)	0.38
	Retinopathy	1.37 (0.48 ~ 3.90)	0.56
	Neuropathy	2.33 (1.03 ~ 5.26)	0.041
	Macroangiopathy	1.70 (0.79 ~ 3.64)	0.18
	MBG[a]	0.51 (0.32 ~ 0.83)	0.006
	CV[a]	1.20 (1.12 ~ 1.30)	< 0.001
	MODD[a]	3.35 (1.49 ~ 7.57)	0.004
	MAGE[a]	1.73 (1.31 ~ 2.28)	< 0.001
	LAGE[a]	1.52 (1.27 ~ 1.82)	< 0.001
	SD[a]	7.50 (3.16 ~ 17.82)	< 0.001
	LBGI[a]	5.46 (2.76 ~ 10.78)	< 0.001

Model χ^2 test $P < 0.001$

CI, confidence interval; CV, coefficient of variation; LAGE, largest amplitude of glycemic excursion; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MBG, mean blood glucose; MODD, mean of daily difference; OR, odds ratio; SD, standard deviation

[a]Measured by the continuous glucose monitoring system

Table 3 Clinical markers of hypoglycemia analyzed by multiple logistic regression

Multiple Model	Dependent variable	OR (95%CI)	*P*
Model 1	MBG[a]	0.46 (0.27 ~ 0.79)	0.005
Model 2	MBG[a]	0.51 (0.32 ~ 0.83)	0.006
	CV[a]	1.20 (1.12 ~ 1.30)	< 0.001
	LBGI[a]	5.46 (2.76 ~ 10.78)	< 0.001
Model 3	MBG[a]	0.58 (0.24 ~ 1.40)	0.22
	MODD[a]	1.34 (0.33 ~ 5.41)	0.68
	LBGI[a]	4.49 (1.91 ~ 10.59)	< 0.001
Model 4	MBG[a]	0.30 (0.12 ~ 0.76)	0.010
	MAGE[a]	2.05 (1.25 ~ 3.36)	0.005
	LBGI[a]	3.49 (1.79 ~ 6.82)	< 0.001
Model 5	MBG[a]	0.35 (0.14 ~ 0.89)	0.027
	LAGE[a]	1.41 (1.05 ~ 1.90)	0.024
	LBGI[a]	2.61 (1.23 ~ 5.53)	0.013
Model 6	MBG[a]	0.17 (0.06 ~ 0.49)	0.001
	SD[a]	27.19 (4.71 ~ 156.83)	< 0.001
	LBGI[a]	2.62 (1.37 ~ 5.00)	0.004

Model 1 was adjusted for age, duration of diabetes, eGFR, Insulin, nephropathy, retinopathy, neuropathy, macroangiopathy, and MBG. Model 2 includes all variables in model 1 plus CV and LBGI. Model 3 includes all variables in model 1 plus MODD and LBGI. Model 4 includes all variables in model 1 plus MAGE and LBGI. Model 5 includes all variables in model 1 plus LAGE and LBGI. Model 6 includes all variables in model 1 plus SD and LBGI

CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LAGE, largest amplitude of glycemic excursion; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MBG, mean blood glucose; MODD, mean of daily difference; OR, odds ratio; SD, standard deviation

[a]Measured by the continuous glucose monitoring system

To address multicollinearity, multivariate logistic regression was conducted for MBG, GV metrics (CV, MAGE, LAGE, MODD, and SD) and LBGI. The analysis revealed that MBG, GV metrics (CV, MAGE, LAGE, and SD), and LBGI remained significant risk factors for hypoglycemia ($p < 0.005$) after adjusted for age, duration of diabetes, eGFR, insulin use, and diabetes complications. In Model 6, MBG (OR = 0.17, 95%CI: 0.06–0.49, $p = 0.001$), SD (OR = 27.19, 95%CI: 4.71–156.83, $p < 0.001$), and LBGI (OR = 2.62, 95%CI: 1.37–5.00, $p = 0.004$) were identified as significant risk factors for hyperglycemia.

Nomogram model to predict the risk of hypoglycemia

Five logistic regression models incorporating hypoglycemia risk factors were analyzed. The AUCs for the models were as follows: MBG-CV-LBGI (0.89, 95% CI: 0.83–0.96,

Table 4 Predictive value of joint CGM-derived metrics for nonhypoglycemia and hypoglycemia

Predictors	AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	cut off
MBG	0.65 (0.55–0.75)	0.35 (0.26–0.45)	0.45 (0.32–0.58)	0.25 (0.13–0.36)	7.25
CV	0.81 (0.73–0.89)	0.76 (0.67–0.83)	0.74 (0.63–0.85)	0.77 (0.66–0.89)	22.06
MODD	0.70 (0.60–0.80)	0.69 (0.60–0.78)	0.66 (0.53–0.78)	0.74 (0.62–0.85)	1.35
MAGE	0.72 (0.63–0.82)	0.68 (0.58–0.76)	0.71 (0.59–0.82)	0.64 (0.51–0.77)	4.15
LAGE	0.77 (0.69–0.86)	0.72 (0.63–0.80)	0.81 (0.71–0.91)	0.62 (0.49–0.75)	9.25
SD	0.77 (0.69–0.86)	0.73 (0.64–0.81)	0.78 (0.67–0.88)	0.68 (0.55–0.80)	1.75
LBGI	0.89 (0.82–0.96)	0.87 (0.80–0.93)	0.90 (0.82–0.97)	0.85 (0.75–0.95)	1.31
MBG-CV-LBGI	0.89 (0.83–0.96)	0.86 (0.78–0.92)	0.90 (0.82–0.97)	0.81 (0.71–0.92)	0.53
MBG-MODD-LBGI	0.89 (0.83–0.96)	0.86 (0.78–0.92)	0.90 (0.82–0.97)	0.81 (0.71–0.92)	0.51
MBG-MAGE-LBGI	0.91 (0.85–0.96)	0.84 (0.76–0.90)	0.91 (0.84–0.99)	0.75 (0.64–0.87)	0.62
MBG-LAGE-LBGI	0.90 (0.84–0.96)	0.86 (0.78–0.92)	0.88 (0.80–0.96)	0.83 (0.73–0.93)	0.51
MBG-SD-LBGI	0.93 (0.88–0.97)	0.85 (0.77–0.91)	0.83 (0.73–0.92)	0.87 (0.78–0.96)	0.44

CV, coefficient of variation; LAGE, largest amplitude of glycemic excursion; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MBG, mean blood glucose; MODD, mean of daily difference; SD, standard deviation

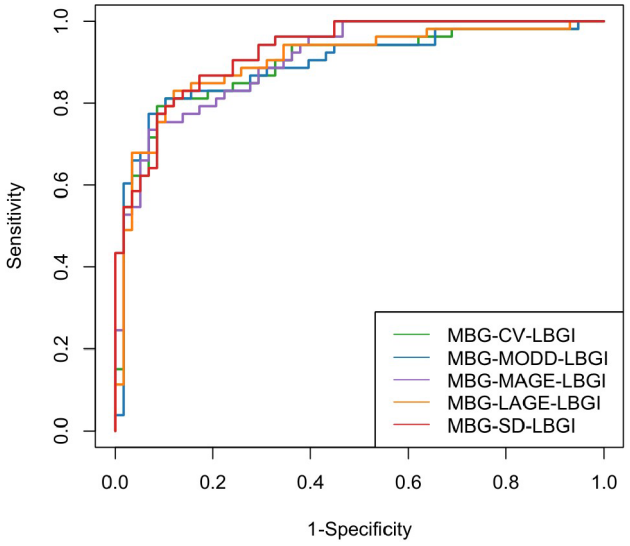

Fig. 2 Receiver operating characteristic curves of joint predictors MBG-CV-LBGI, MBG-MODD-LBGI, MBG-MAGE-LBGI, MBG-LAGE-LBGI, and MBG-SD-LBGI models for predicting hypoglycemia in patients with type 2 diabetes with TIR>70%. CV, coefficient of variation; LAGE, largest amplitude of glycemic excursion; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MBG, mean blood glucose; MODD, mean of daily difference; SD, standard deviation

$p<0.001$), MBG-MODD-LBGI (0.89, 95% CI: 0.83–0.96, $p<0.001$), MBG-MAGE-LBGI (0.91, 95% CI: 0.85–0.96, $p<0.001$), MBG-LAGE-LBGI (0.90, 95% CI: 0.84–0.96, $p<0.001$), and MBG-SD-LBGI (0.93, 95% CI: 0.88–0.97, $p<0.001$) (Table 4;Fig. 2). Among these, MBG-SD-LBGI demonstrated the best predictive capability.

A nomogram model was constructed based on the three predictors (MBG, SD, and LBGI) (Fig. 3). The total score was calculated by summing the corresponding scores of MBG, SD, and LBGI, and the probability of hypoglycemia was derived from the total score. Calibration plots indicated strong agreement between observed and predicted probabilities (mean absolute error = 0.021). The Hosmer-Lemeshow test confirmed good calibration accuracy ($X^2 = 2.822$, $p = 0.945$) (Fig. 4). Furthermore, the DCA suggested that the nomogram model could provide clinical benefits for patients at risk of hypoglycemia (Fig. 5).

Discussion

The role of tight glycemic control in preventing diabetes complications has been well established [24, 25]. However, intensive glycemic control strategies significantly increase the risk of hypoglycemia, posing a considerable obstacle to achieving optimal glycemic control in individuals with diabetes [26]. Previous studies have reported that even among patients with well-controlled HbA1c levels, the incidence of hypoglycemia episodes can be as high as 48.0% [16]. Current clinical guidelines recommend a target TIR of at least 70% for patients with T2DM [27], but limited research focuses on hypoglycemic episodes and the contributing factors in patients who achieve this target.

This study is the first to report the occurrence of hypoglycemic episodes identified by CGM-derived data in this specific population. Among patients with T2DM who achieved a TIR > 70%, 47.75% experienced level 1 hypoglycemia (glucose < 3.9 mmol/L) and 18.92% experienced level 2 hypoglycemia (glucose < 3.0 mmol/L). Although all participants met the TBR targets (TBR level 1 < 4% and TBR level 2 < 1%), the hypoglycemic group showed mean TBR percentages of 5.26% and 1.19% for levels 1 and 2, respectively, exceeding the recommended thresholds. Our study also found that hypoglycemia occurred more

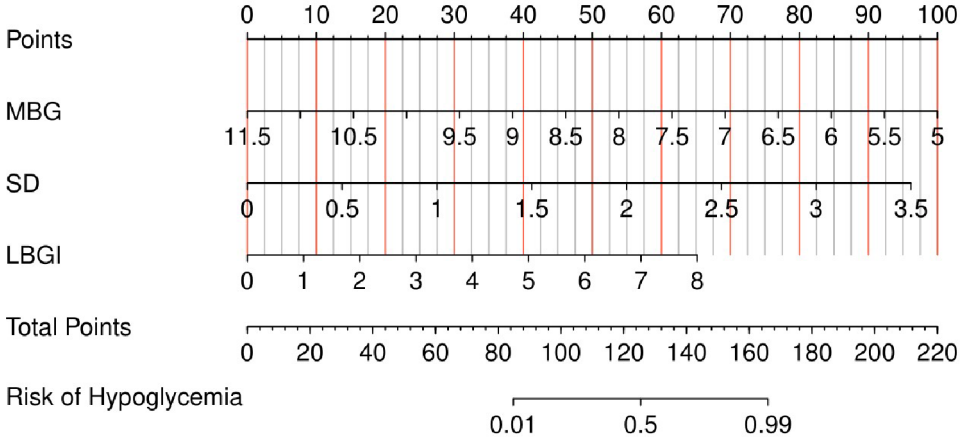

Fig. 3 A nomogram model for predicting hypoglycemia in patients with type 2 diabetes with TIR >70%

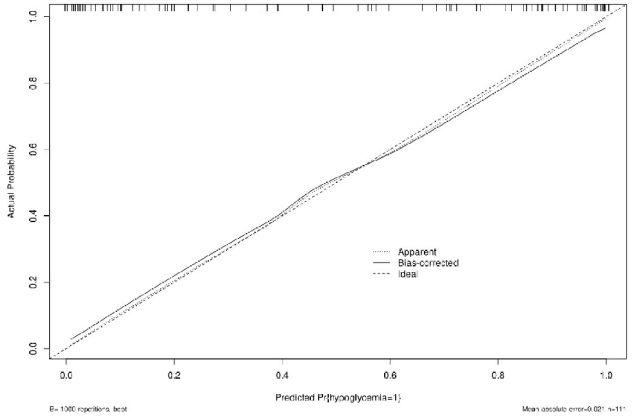

Fig. 4 The calibration curve of prediction model for hypoglycemia in patients with type 2 diabetes with TIR >70%

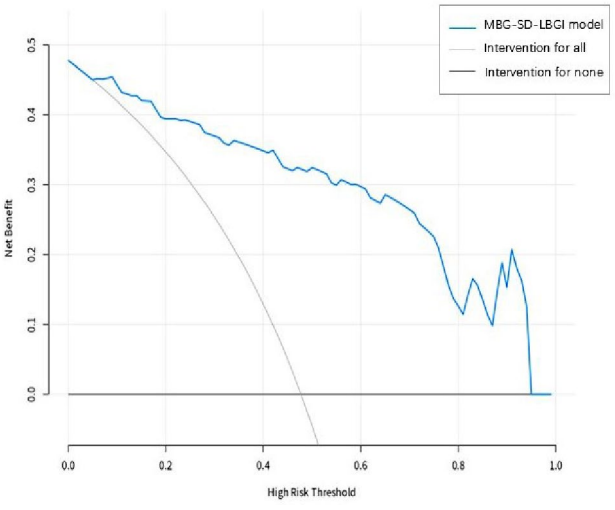

Fig. 5 The decision curve of prediction model for hypoglycemia in patients with type 2 diabetes with TIR >70%, illustrating the net benefit of the model at various threshold probabilities

frequently at night compared to daytime periods. Therefore, nighttime monitoring or therapy adjustments are also recommended for T2DM patients with TIR > 70%. These findings highlight that hypoglycemia remains prevalent among patients with well-controlled TIR, underscoring the importance of careful management in such cases. Further research should aim to identify specific risk factors associated with hypoglycemia and stratify high-risk patients for targeted interventions.

With advancements in glucose monitoring technologies, CGM-derived metrics such as TIR, TBR, time above range (TAR), GV, and glycemic risk indices have become valuable tools in glycemic management. As a complement to HbA1c, these metrics help clinicians and patients make more informed, personalized management decisions. Among the GV metrics—SD, CV, MAGE, MODD, and LAGE—several have been identified as potential predictors of hypoglycemia [28]. For instance, Monnier et al. found a strong correlation between MBG, SD, and hypoglycemia [29], while Torimoto et al. reported that low MBG and high CV were predictors of hypoglycemia in patients with T2DM [22]. Gómez et al. proposed a CV value of 34% as a marker for hypoglycemia risk in T2DM patients [30]. Despite these findings, establishing a standardized GV metric for universal clinical use remains a challenge.

Our study specifically examined T2DM patients with well-controlled glycemia (TIR > 70%) and found a consistent relationship between GV metrics and hypoglycemia. Among these, MBG, SD, and LBGI were the most reliable predictors. SD, in particular, provided a robust and independent assessment of GV, facilitating better differentiation of hypoglycemia risk in this population. While some studies favor CV for its reduced sensitivity to mean glucose fluctuations and HbA1c levels [31], others advocate for MAGE due to its longstanding use [32] and emphasis on significant glucose excursions [33]. Metrics like MODD offer detailed analyses of glucose variations

over periods ranging from hours to days, but their clinical utility remains under debate [34]. In this study, SD was both measured through CGM and calculated from self-monitoring of blood glucose (SMBG) data, making it a practical choice for routine medical practice. Combining MBG, SD, and TIR offers clinicians a more comprehensive perspective on glycemic control, enabling more accurate hypoglycemia risk assessments and tailored diabetes management.

This study also evaluated glycemic risk indices derived from CGM, such as the LBGI and HBGI, which estimate hypoglycemic or hyperglycemic risk based on prior glucose patterns and a mathematical adjustment for the skewness of blood glucose levels. LBGI has been shown to correlate strongly with severe hypoglycemia and is higher in individuals with a history of such events. Consistent with prior research by Kovatchev et al., which identified an LBGI threshold of greater than 5 as a marker for severe hypoglycemia [35], our findings confirm the utility of LBGI in detecting hypoglycemia in patients with T2DM who achieved TIR above 70%.

Despite the growing number of proposed CGM metrics, few studies have combined these metrics to accurately predict hypoglycemia in T2DM patients with well-controlled TIR [36]. For instance, Han et al. developed a 14-variable nomogram to predict severe hypoglycemia in T2DM patients [37], and another study used a nomogram to assess hypoglycemia risk in patients treated with insulin pumps during enteral nutrition [38]. Montaser et al. proposed a two-dimensional framework for glycemic assessment in diabetes (both T1DM and T2DM), identifying treatment efficacy (quantified by hyperglycemia metrics: MG, TAR, TAR2) and treatment safety (measured by hypoglycemia metrics: TBR, TBR2, CV) as the fundamental dimensions [39]. Although their study didn't specifically validate the AUC for hypoglycemia prediction, their safety dimension (second principal component) presents a potential foundation for streamlined modeling approaches. In contrast, our MBG-SD-LBGI model achieved higher predictive accuracy (AUC = 0.93) for hypoglycemia detection in T2DM patients with TIR > 70%, making it more suitable for scenarios requiring high-precision risk identification. Future research should investigate whether using Montaser's safety dimension metrics (TBR, TBR2, and CV) can achieve comparable predictive accuracy while offering greater simplicity. The nomogram constructed using these indicators provides individualized risk assessments, enabling clinicians to select appropriate interventions. The DCA further demonstrated the clinical utility of this model, underscoring its potential benefits in managing hypoglycemia.

To our knowledge, this is the first study to develop a nomogram model for predicting the risk of hypoglycemia among T2DM patients with well-controlled TIR based on CGM-derived metrics. Notably, nearly half of these patients experienced hypoglycemia, as detected by CGM, highlighting the importance of incorporating CGM in diabetes management. While the consensus defines a hypoglycemia episode as lasting at least 15 min, we adopted a threshold of < 3.9 mmol/L for a minimum of 5 min based on a previously published study [22]. This shorter duration allows for earlier and more sensitive detection of hypoglycemia in this specific population with TIR in target. However, the study has several limitations. Its retrospective and cross-sectional design, coupled with a small sample size, limits the ability to analyze the effects of specific medications and dosages. Although no statistical difference in sulfonylurea use was observed between groups, the small sample size may have influenced this result. Also, insulin regimens should indeed be carefully considered and tailored based on individual patient factors, including their insulin sensitivity, meal patterns, and risk for hypoglycemia. Further research is needed to explore which specific insulin regimens are most effective at reducing the risk of hypoglycemia while maintaining optimal glycemic control in patients targeting a TIR > 70%. Secondly, owing to the inherent characteristics of the observational study design, it is unlikely to entirely eliminate possible residual confounding from unknown or unmeasured confounders. However, we carefully adjusted for potential confounding factors. Future research should focus on adopting prospective study designs and incorporating adjustments for factors such as dietary intake, physical activity patterns, and medication adherence to enhance the stability and reliability of our findings. Thirdly, there are two basic types of CGM devices: those that are owned by the user, including real-time CGM (rtCGM) and intermittently scanned CGM (isCGM); and professional CGM devices that are owned and applied in the clinic [40]. The iPro^{TM}2 system (Medtronic) used in this study is a professional CGM device. A network meta-analysis demonstrated that rtCGM was ranked highest for HbA1c reduction and TIR/TAR optimization compared to professional CGM, isCGM, and SMBG [41]. The heterogeneity among different CGMs may affect the results; therefore, the applicability of the study findings to other types of CGMs should be interpreted with caution. Additionally, while a seven-day CGM monitoring period was used, current consensus recommends at least 10–14 days for comprehensive analysis in patients with T1DM [42]. However, previous research has shown minimal difference between glucose management indicator (GMI) calculated using 7-day and 14-day CGM data [43]. Considering the stable glycemic control and lower GV in our T2DM cohort compared to patients with T1DM, the 7-day duration is deemed sufficient for this study. Future studies using a 2-week

monitoring period may help validate and strengthen these findings.

Conclusion

Nearly half of patients with T2DM who met the target of TIR > 70% experienced hypoglycemia episodes as identified by CGM. CGM-derived metrics showed a significant correlation with hypoglycemia in this specific patient population. Among the models evaluated, the MBG-CV-LBGI model demonstrated strong predictive capability, simplicity, and practical utility, making it an effective tool for early hypoglycemia risk prediction.

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Author contributions
Wen Xu, Daizhi Yang, and Jinhua Yan were primarily responsible for the study design, interpretation of data analyses and the discussion. Jianwen Lu and Danrui Chen contributed to data analyses and wrote the manuscript. Beisi Lin and Zhigu Liu contributed to data collection and interpretation of the data. Yanling Yang contributed to the discussion. Ling He revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (IRB No. [2020] 02-107-01) and has been performed under the guidelines of the Helsinki Declaration. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Effect of intensive. blood-glucose control with Metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK prospective diabetes study (UKPDS) group. Lancet (London England). 1998;352(9131):854–65.
2. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103–17.
3. Hypoglycemia in the Diabetes Control and Complications Trial. The diabetes control and complications trial research group. Diabetes. 1997;46(2):271–86.
4. Defining. Reporting hypoglycemia in diabetes: a report from the American diabetes association workgroup on hypoglycemia. Diabetes Care. 2005;28(5):1245–9.
5. Zhang J, He X, Zhang L, Wang K, Chen H, Wu J. Association of severe hypoglycemia with all-cause mortality and complication risks among patients with type 2 diabetes mellitus in China. Diabetes Res Clin Pract. 2020;170:108493.
6. Stone MP, Agrawal P, Chen X, Liu M, Shin J, Cordero TL, Kaufman FR. Retrospective analysis of 3-Month Real-World glucose data after the minimed 670G system commercial launch. Diabetes Technol Ther. 2018;20(10):689–92.
7. Monnier L, Colette C. Glycaemic variability and ambient hyperglycaemia: how and when are they linked? Diabetes Metab. 2014;40(4):237–40.
8. Chilelli NC, Burlina S, Sartore G, Lapolla A. Between reduction of glucose fluctuations and increased therapeutic adherence: an example of the benefits of vildagliptin in an elderly diabetic patient. Aging Clin Exp Res. 2015;27(1):85–7.
9. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA(1c) alone to assess glycemic control can be misleading. Diabetes Care. 2017;40(8):994–9.
10. Qu Y, Jacober SJ, Zhang Q, Wolka LL, DeVries JH. Rate of hypoglycemia in insulin-treated patients with type 2 diabetes can be predicted from glycemic variability data. Diabetes Technol Ther. 2012;14(11):1008–12.
11. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Ólafsdóttir AF, Frid A, Wedel H, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA. 2017;317(4):379–87.
12. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA. 2017;317(4):371–8.
13. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care. 2019;42(3):400–5.
14. 6. Glycemic targets: standards of medical care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S73–84.
15. Advani A. Positioning time in range in diabetes management. Diabetologia. 2020;63(2):242–52.
16. Jing Ma CT, Li Zhong D, Chen C, Wang G, Liu X, Ran. Evaluation of hypoglycemia in type 2 diabetic patients with well-controlled glucose levels by continuous glucose monitoring system. Chin J Diabetes Mellitus. 2017;09(7):428–34.
17. Dawnbringer J, Hill H, Lundgren M, Catrina SB, Caballero-Corbalan J, Cederblad L, Carlsson PO, Espes D. Development of a three-dimensional scoring model for the assessment of continuous glucose monitoring data in type 1 diabetes. BMJ Open Diabetes Res Care 2024, 12(4).
18. Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, Kerr D, Ahn D, Peters AL, Umpierrez GE, et al. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. J Diabetes Sci Technol. 2023;17(5):1226–42.
19. Piersanti A, Morettini M, Cristino S, Giudice LLD, Burattini L, Mosconi G, Göbl CS, Mambelli E, Tura A. Assessing hypoglycemia risk during Hemodialysis using an explainable machine learning approach based on continuous glucose monitoring metrics. Biomed Signal Process Control. 2025;102:107319.
20. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, et al. Estimating glomerular filtration rate from serum creatinine and Cystatin C. N Engl J Med. 2012;367(1):20–9.
21. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol Ther. 2009;11(Suppl 1):S55–67.
22. Torimoto K, Okada Y, Hajime M, Tanaka K, Tanaka Y. Risk factors of hypoglycemia in patients with type 2 diabetes mellitus: A study based on continuous glucose monitoring. Diabetes Technol Ther. 2018;20(9):603–12.
23. Alfieri V, Myasoedova VA, Vinci MC, Rondinelli M, Songia P, Massaiu I, Cosentino N, Moschetta D, Valerio V, Ciccarelli M et al. The role of glycemic variability in cardiovascular disorders. Int J Mol Sci 2021, 22(16).
24. Intensive blood-glucose. Control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type

2 diabetes (UKPDS 33). UK prospective diabetes study (UKPDS) group. Lancet (London England). 1998;352(9131):837–53.
25. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
26. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med. 2015;175(3):356–62.
27. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–603.
28. Gehlaut RR, Dogbey GY, Schwartz FL, Marling CR, Shubrook JH. Hypoglycemia in type 2 Diabetes–More common than you think: A continuous glucose monitoring study. J Diabetes Sci Technol. 2015;9(5):999–1005.
29. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. Diabetes Technol Ther. 2011;13(8):813–8.
30. Gómez AM, Muñoz OM, Marin A, Fonseca MC, Rondon M, Robledo Gómez MA, Sanko A, Lujan D, García-Jaramillo M, León Vargas FM. Different indexes of glycemic variability as identifiers of patients with risk of hypoglycemia in type 2 diabetes mellitus. J Diabetes Sci Technol. 2018;12(5):1007–15.
31. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. Postgrad Med. 2011;123(4):107–18.
32. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes. 1970;19(9):644–55.
33. Service FJ. Glucose variability. Diabetes. 2013;62(5):1398–404.
34. Schlichtkrull J, Munck O, Jersild M. [M-VALUE, AN INDEX FOR BLOOD SUGAR CONTROL IN DIABETICS]. Ugeskr Laeger. 1964;126:815–20.
35. Kovatchev BP, Cox DJ, Farhy LS, Straume M, Gonder-Frederick L, Clarke WL. Episodes of severe hypoglycemia in type 1 diabetes are preceded and followed within 48 hours by measurable disturbances in blood glucose. J Clin Endocrinol Metab. 2000;85(11):4287–92.
36. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, Lu W, Zhu W, Bao Y, Vigersky RA, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. Diabetes Care. 2018;41(11):2370–6.
37. Han K, Yun JS, Park YM, Ahn YB, Cho JH, Cha SA, Ko SH. Development and validation of a risk prediction model for severe hypoglycemia in adult patients with type 2 diabetes: a nationwide population-based cohort study. Clin Epidemiol. 2018;10:1545–59.
38. Wu J, Wu J, Zhou Y, Lu X, Zhao W, Xu F. Nomogram for predicting hypoglycemia in type 2 diabetes mellitus patients treated with insulin pump during enteral nutrition. Diabetes Metabolic Syndrome Obesity: Targets Therapy. 2024;17:2147–54.
39. Montaser E, Fabris C, Kovatchev B. Essential continuous glucose monitoring metrics: the principal dimensions of glycemic control in diabetes. Diabetes Technol Ther. 2022;24(11):797–804.
40. 7. Diabetes technology: standards of medical care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S97–112.
41. Lu J, Ying Z, Wang P, Fu M, Han C, Zhang M. Effects of continuous glucose monitoring on glycaemic control in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2024;26(1):362–72.
42. Bugler J. An estimation of the amount of data required to measure glycaemic variability (Abstract). In: Proceedings 1st ATTD. In: *Meeting, Prague.* vol. 55; 2008.
43. Bailey R, Calhoun P, Bergenstal RM, Beck RW. Assessment of the glucose management Indicator using different sampling durations. Diabetes Technol Ther. 2023;25(2):148–50.

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