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Original Research Article

Impact of Glycaemic Variability on Clinical Outcomes in Hospitalised Diabetic Patients with Acute Illness

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ABSTRACT

Background: Dynamic glucose fluctuations - termed glycaemic variability (GV) - may predict adverse clinical outcomes beyond mean glucose in hospitalised patients. Hospital-based data from general medical wards in South Asian settings are scarce.
Objectives: To examine the association between inpatient GV and composite adverse outcomes in diabetic patients with acute illness, after adjusting for illness severity.
Methods: Prospective cohort study at SAL Hospital, Ahmedabad (November 2025–April 2026; N=312 T2DM patients). GV was quantified by coefficient of variation (CV%), standard deviation (SD), mean amplitude of glycaemic excursions (MAGE), time in range (TIR), and mean of daily differences (MODD) from ≥4 daily point-of-care readings. Primary outcome: pre-specified composite of mortality, unplanned ICU admission, sepsis, AKI stage ≥2, or cardiovascular event. Analyses: Kruskal-Wallis with Dunn–BH post-hoc, multivariable logistic regression adjusted for APACHE II, SOFA, and Charlson Comorbidity Index, Kaplan-Meier with log-rank test, and ROC analysis with DeLong 95%CI.
Results: The composite adverse outcome occurred in 126 of 312 patients (40.4%). After adjustment for APACHE II, SOFA score, Charlson index, admission HbA1c, and age, CV ≥36% was independently associated with the composite outcome (adjusted OR 3.68; 95%CI 2.18–6.22; $p<0.001$). MAGE ≥70 mg/dL (OR 3.12; 1.86–5.23) and any hypoglycaemia episode (OR 2.64; 1.58–4.40) were also independently associated. CV% achieved AUC 0.847 (95%CI 0.796–0.898) for composite outcome prediction. Log-rank analysis confirmed significantly different adverse-event-free survival across GV tertiles ($\chi^2=48.6$; $p<0.001$).
Conclusions: High GV, indexed by CV% and MAGE, is independently associated with adverse clinical outcomes in hospitalised T2DM patients after adjusting for illness severity. These associations suggest that systematic inpatient GV monitoring may warrant prospective evaluation as part of structured diabetes care.

Keywords*: glycaemic variability; coefficient of variation; MAGE; inpatient diabetes; acute illness; clinical outcomes; prospective cohort; observational study.*

INTRODUCTION

The management of hyperglycaemia in hospitalised patients has been a major focus of clinical research over the past two decades. Landmark trials, including NICE-SUGAR and the Leuven studies, established that both sustained hyperglycaemia and iatrogenic hypoglycaemia are associated with increased in-hospital mortality, infectious complications, and prolonged length of stay.[1,2] However, these studies primarily targeted mean blood glucose values, treating glycaemic control as a static, time-averaged measure. A growing body of evidence now suggests that dynamic glucose fluctuations - collectively termed glycaemic variability (GV) - may be independently associated with adverse outcomes beyond that attributable to mean glucose alone.[3]

GV encompasses multiple dimensions of glucose behaviour including the amplitude of excursions above and below the target range, the frequency of oscillations, inter-day variation, and the proportion of time spent within a physiologically safe band. Several validated metrics operationalise these dimensions: the coefficient of variation (CV%, defined as SD÷mean glucose×100), mean amplitude of glycaemic excursions (MAGE), time in range (TIR: percentage of readings 70–180 mg/dL), standard deviation (SD), and mean of daily differences (MODD). Among these, CV% has particular

clinical traction because it is dimensionless, adjusts for mean glucose, and a threshold of ≥36% has been proposed as a clinically meaningful marker of 'unstable glucose control'.[5]

The biological basis linking GV to tissue injury includes: reactive oxygen species generation through mitochondrial electron transport uncoupling during rapid glucose oscillations; NF-κB activation in endothelial cells promoting a pro-inflammatory milieu; impairment of neutrophil phagocytic function; and sympathoadrenal activation, QTc prolongation, and platelet aggregation during hypoglycaemic episodes.[6,7,8] A critical limitation in this mechanistic literature is that GV may partly reflect underlying illness severity — sicker patients may have both greater glucose dysregulation and worse outcomes. Adjusting for validated severity scores (APACHE II, SOFA, Charlson Comorbidity Index) is therefore essential.

Despite mechanistic plausibility, systematic multi-metric GV monitoring in general medical inpatient settings in India remains uncommon. The present prospective cohort study at SAL Institute of Medical Sciences, Ahmedabad, aimed to: (1) quantify GV using five validated metrics; (2) examine the association between GV and a pre-specified composite adverse outcome after adjusting for illness severity; (3) identify optimal GV thresholds by ROC analysis; and (4) explore the association of individual GV metrics with specific adverse outcome domains.

MATERIALS AND METHODS

This manuscript is reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies.

Study Design and Setting

Prospective single-centre observational cohort study. Department of Internal Medicine, SAL Institute of Medical Sciences (SAL Hospital) Ahmedabad , Gujarat, India. Data collection: 1 November 2025 – 30 April 2026 (6 months).

Participants

Inclusion criteria

- Confirmed T2DM (ADA 2024 diagnostic criteria, physician-confirmed with medical record documentation) or newly diagnosed (HbA1c ≥6.5% or glucose ≥200 mg/dL with symptoms) admitted with acute illness (sepsis, pneumonia, ACS, stroke, AKI, acute exacerbation of chronic disease, polytrauma, or other acute medical condition).
- Age ≥18 years; anticipated hospitalisation ≥48 hours to allow collection of ≥8 POC glucose readings.
- Written informed consent in patient's preferred language (Gujarati, Hindi, or English).

Exclusion criteria

- Type 1 DM (C-peptide <0.6 ng/mL or DKA at onset <25 years); gestational diabetes; secondary diabetes (pancreatic, drug-induced).
- Patients admitted directly to palliative care or with withdrawal of active treatment on Day 1.
- Continuous glucose monitoring (CGM) device already in situ (to avoid data heterogeneity).
- Severe aphasia or cognitive impairment precluding informed consent; patient refusal.

Glucose Monitoring Protocol

All enrolled patients underwent standardised point-of-care (POC) capillary blood glucose monitoring (Accu-Chek Guide, Roche Diagnostics; calibrated per ISO 15197:2013) at four fixed time-points daily: pre-breakfast (06:00–07:00), pre-lunch (11:30–12:30), pre-dinner (17:00–18:00), and 22:00 hours. Additional readings were obtained for clinical indications. Nursing staff received standardised technique training before the study commenced; daily quality-control checks were performed using manufacturer-supplied control solutions. All POC values were electronically entered into the IntelliCare EMR system, which exported a structured dataset for GV calculation.

GV metrics were calculated for the full hospitalisation period using validated algorithms: (1) CV% = (SD ÷ mean glucose) × 100, with CV ≥36% pre-specified as 'high GV' per Kovatchev et al.[5]; (2) SD = population standard deviation of all POC readings; (3) MAGE = mean absolute difference between consecutive glucose peaks and nadirs exceeding one SD from the mean, calculated per Service et al.[9]; (4) TIR = percentage of readings within 70–180 mg/dL; (5) MODD = mean absolute difference between glucose values at identical time-points on consecutive days, per Molnar et al.[10]

Assessment of Illness Severity

Three validated illness severity instruments were recorded for all patients within 24 hours of admission and used as pre-specified confounders in the logistic regression model: (1) APACHE II (Acute Physiology and Chronic Health Evaluation II) — scored using worst values in the first 24 hours; higher scores indicate greater severity; (2) SOFA (Sequential Organ Failure Assessment) — summed across six organ systems, scored at admission; (3) Charlson Comorbidity Index — calculated using standard weightings per Charlson et al. 1987, summarising the burden of co-existing conditions.

Outcome Definitions

Primary outcome (composite adverse endpoint): the occurrence of any of the following during the index hospitalisation: in-hospital mortality; unplanned transfer to the intensive care unit (ICU); sepsis or septic shock (Sepsis-3 definitions, Singer et al. 2016)[22]; acute kidney injury (AKI) stage ≥2 per KDIGO 2022 criteria[21]; or new cardiovascular event (STEMI, NSTEMI, stroke, or acute decompensated heart failure).

Rationale for composite outcome: each component is a clinically important manifestation of acute critical illness in diabetic patients. Composites are used in observational studies to increase event rates and statistical power in moderately-sized cohorts. All five components were pre-specified a priori based on established associations between GV and organ injury in prior literature.[3,6,7]

Secondary outcomes: each composite component independently; hospital LOS; 30-day readmission; occurrence of any hypoglycaemia episode (POC glucose <70 mg/dL).

Sample Size

The sample size was calculated for the primary analysis (logistic regression with composite outcome as binary endpoint). Based on an estimated composite adverse event rate of 35% in hospitalised T2DM patients,[3] an expected OR of 2.5 for CV% ≥36% vs. <22%, and 8 predictors (events-per-variable ratio ≥10), the minimum required number of events was 126 (implying n ≥360 at 35% event rate). Anticipating 10% dropout: target enrolment 400; enrolled 398; analysed 312 after exclusions. This sample provided adequate power for the primary logistic regression analysis.

Statistical Analysis

Analyses were performed using R v4.3.2. Statistical significance threshold: $p<0.05$, two-tailed throughout.

Descriptive statistics: continuous variables as mean (SD) or median [IQR] per Shapiro-Wilk normality test; categorical as n (%). GV tertiles were defined by SD of POC glucose: T1 <22 mg/dL (low GV), T2 22–40 mg/dL (moderate GV), T3 >40 mg/dL (high GV). Between-tertile comparisons: Kruskal-Wallis test with pairwise Dunn tests (Benjamini-Hochberg false discovery correction).

Multivariable logistic regression (primary analysis): the outcome variable was the composite adverse endpoint (binary). Pre-specified predictor variables were entered simultaneously: CV% (primary GV metric; categorical at ≥36% vs. <22%), MAGE (categorical at ≥70 mg/dL), any hypoglycaemia episode, APACHE II score (continuous, per 5-unit increment), SOFA score (≥6 vs. <6), Charlson Comorbidity Index (≥3 vs. <3), admission HbA1c (≥9% vs. <9%), and age (≥65 vs. <65 years). ICU admission was deliberately excluded from the predictor set as it is a component of the composite outcome (circular reasoning). Due to high inter-correlations between GV metrics (Spearman ρ up to 0.88; Table 5), the five GV metrics were not entered simultaneously. CV% was pre-selected as the primary GV metric based on published evidence and clinical interpretability; MAGE and hypoglycaemia were entered as theoretically distinct constructs (oscillation amplitude and lower glycaemic boundary respectively). Collinearity was confirmed acceptable (VIF <3.0 for all variables). Cook's D was assessed for influential observations (threshold 4/n). Model calibration: Hosmer-Lemeshow test. Discrimination: AUC-ROC (DeLong 1988 method)[23]; 10-fold stratified cross-validation (5 repeats, seed=99).

Time-to-event analysis: Kaplan-Meier curves for time to first adverse event, stratified by GV tertile. Log-rank test for overall comparison (Breslow test for early event differences). Time origin: date of enrolment. Event: first occurrence of any composite outcome component. Censoring: hospital discharge without event, or 30-day follow-up without event.

Note on Cox proportional hazards: Cox regression was considered for the primary analysis but was not applied as the primary model because: (1) hospital LOS is short (median 7 days), limiting time-varying hazard estimation; (2) the logistic regression model provides a simpler, more interpretable measure of outcome association appropriate to this study. Kaplan-Meier curves with log-rank test are used descriptively to illustrate survival differences across tertiles.

ROC analysis: AUC for each GV metric individually (DeLong 95%CI); pairwise DeLong comparisons; Youden index for optimal cutoff determination; sensitivity, specificity, PPV, NPV reported.

Correlation matrix: Spearman's rank coefficient for inter-metric and LOS associations; Bonferroni-corrected $\alpha = 0.0024$ (21 pairwise tests). High inter-metric correlations confirmed that simultaneous regression entry would be inappropriate.

Ethics and Trial Registration

Ethics approval was granted by the Institutional Ethics Committee, SAL Institute of Medical Sciences. The study was conducted in accordance with the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants. Data were de-identified and stored on encrypted institutional servers with access restricted to named investigators.

RESULTS

Participant Flow and Baseline Characteristics

Of 398 screened patients, 86 were excluded (34 Type 1/secondary DM, 18 anticipated stay <48 h, 16 declined consent, 10 CGM in situ, 8 palliative Day 1), yielding N=312 for analysis. All completed ≥8 POC glucose readings (median 28 [IQR 22–36] per patient). Thirty-day follow-up was obtained for 298 of 312 (95.5%). No patients were lost to follow-up for the primary in-hospital endpoint. Baseline characteristics by GV tertile are shown in Table 1.

Mean age was 58.4 (SD 14.2) years; 55.1% male. APACHE II scores differed significantly across tertiles (T1: 12.4 vs. T3: 17.1; Kruskal-Wallis $p<0.001$), confirming that high-GV patients were also sicker — the key reason why illness severity adjustment was essential. Charlson Comorbidity Index and SOFA scores also increased progressively across tertiles (all

p<0.001). GV metrics showed expected between-tertile separation (all Kruskal-Wallis p<0.001; Dunn–BH pairwise all p<0.05).

Table 1. Baseline Characteristics, Illness Severity, and GV Metrics by Tertile (N=312)

Variable	Total (N=312)	Low GV — T1 (n=104)	Moderate GV — T2 (n=104)	High GV — T3 (n=104)
Demographics				
Age (years): mean (SD)	58.4 (14.2)	57.1 (13.8)	58.6 (14.4)	59.4 (14.3)
Sex: male, n (%)	172 (55.1)	58 (55.8)	56 (53.8)	58 (55.8)
T2DM duration (years): mean (SD)	11.2 (7.6)	9.4 (6.8)	11.4 (7.6)	12.8 (8.1)
BMI (kg/m²): mean (SD)	27.1 (4.4)	26.8 (4.1)	27.0 (4.4)	27.4 (4.6)
Illness Severity Scores (pre-specified confounders)				
APACHE II score: mean (SD)	14.8 (6.4)	12.4 (5.8)*	14.9 (6.2)*	17.1 (6.8)*
SOFA score: mean (SD)	4.2 (2.8)	3.2 (2.4)*	4.3 (2.7)*	5.1 (3.0)*
Charlson Comorbidity Index: mean (SD)	3.8 (1.9)	3.4 (1.8)*	3.8 (1.9)*	4.2 (1.9)*
Charlson Comorbidity Index ≥3, n (%)	184 (59.0)	52 (50.0)	62 (59.6)	70 (67.3)
Admission Glycaemic Status				
Admission glucose (mg/dL): mean (SD)	218.6 (88.4)	178.4 (64.2)*	221.8 (88.2)*	255.8 (98.1)*
Admission HbA1c (%): mean (SD)	9.2 (2.1)	8.1 (1.8)*	9.3 (2.0)*	10.2 (2.3)*
Pre-existing insulin use, n (%)	104 (33.3)	28 (26.9)	34 (32.7)	42 (40.4)
GV Metrics During Hospitalisation				
SD of glucose (mg/dL): mean (SD)	29.4 (14.8)	16.2 (4.1)*	29.8 (5.4)*	44.2 (8.6)*
CV (%): mean (SD)	22.8 (11.4)	13.2 (3.2)*	23.1 (4.4)*	32.1 (5.6)*
MAGE (mg/dL): mean (SD)	52.4 (24.8)	28.8 (8.2)*	52.8 (10.6)*	75.6 (14.2)*
TIR 70–180 mg/dL (%): mean (SD)	62.4 (18.8)	78.4 (9.2)*	62.1 (8.8)*	46.8 (11.4)*
MODD (mg/dL): mean (SD)	28.4 (14.2)	16.4 (5.2)*	28.8 (6.4)*	40.2 (8.8)*
Any hypoglycaemia episode (<70 mg/dL), n (%)	78 (25.0)	12 (11.5)	24 (23.1)	42 (40.4)

*T1=Low GV (SD<22 mg/dL); T2=Moderate GV (SD 22–40); T3=High GV (SD>40). *Kruskal-Wallis p<0.001 across tertiles; all pairwise Dunn–BH tests p<0.05. APACHE II and SOFA scores recorded within 24 hours of admission. Charlson Comorbidity Index calculated per Charlson et al. (1987). CV=Coefficient of Variation; MAGE=Mean Amplitude of Glycaemic Excursions; TIR=Time in Range; MODD=Mean of Daily Differences. No missing data on primary outcome or listed covariates.*

*Kruskal-Wallis p<0.001 across tertiles with Dunn–BH pairwise p<0.05. APACHE II and SOFA recorded within 24 hours of admission.

Clinical Outcomes by GV Tertile

The composite adverse outcome occurred in 126 patients (40.4%), rising across tertiles: T1 25.0%, T2 40.4%, T3 55.8% (chi-square p<0.001). In-hospital mortality was 5.8% in T1 vs. 19.2% in T3 (p<0.001). Sepsis occurred in 7.7% of T1 vs. 25.0% of T3 patients. AKI was present in 17.3% of T1 vs. 44.2% of T3. Median LOS was 5 [3–8] days in T1 vs. 10 [7–16] days in T3 (p<0.001). Detailed outcomes are in Table 2; GV metric comparisons by outcome group are shown in Figure 1.

Table 2. Clinical Outcomes Stratified by GV Tertile (N=312)

Outcome	Total (N=312)	T1 Low GV (n=104)	T2 Mod GV (n=104)	T3 High GV (n=104)
In-hospital mortality†, n (%)	**38 (12.2)**	**6 (5.8)**	**12 (11.5)**	**20 (19.2)**
Unplanned ICU admission†, n (%)	**86 (27.6)**	**18 (17.3)**	**26 (25.0)**	**42 (40.4)**
Infectious complications, n (%)	112 (35.9)	24 (23.1)	38 (36.5)	50 (48.1)
— Hospital-acquired infection†	58 (18.6)	10 (9.6)	18 (17.3)	30 (28.8)
— Sepsis / septic shock†	48 (15.4)	8 (7.7)	14 (13.5)	26 (25.0)
Acute kidney injury (KDIGO ≥1)†, n (%)	96 (30.8)	18 (17.3)	32 (30.8)	46 (44.2)
Cardiovascular event†, n (%)	44 (14.1)	8 (7.7)	14 (13.5)	22 (21.2)
Prolonged LOS (>7 days), n (%)	128 (41.0)	28 (26.9)	44 (42.3)	56 (53.8)
Hospital LOS (days): median [IQR]	7 [4–12]	5 [3–8]	7 [5–11]	10 [7–16]
30-day readmission, n (%)	62 (19.9)	14 (13.5)	20 (19.2)	28 (26.9)
Composite adverse outcome‡, n (%)	**126 (40.4)**	**26 (25.0)**	**42 (40.4)**	**58 (55.8)**

†Components of the composite adverse outcome (‡). ‡Composite = in-hospital mortality OR unplanned ICU admission OR sepsis/septic shock OR AKI stage ≥2 OR cardiovascular event during admission. Composite outcomes are commonly used in clinical trials and observational studies to maximise event rates in moderately-sized studies; components were selected a priori based on established clinical relevance to glycaemic dysregulation. All between-tertile comparisons: chi-square (categorical) or Kruskal-Wallis (continuous), all p<0.001 except 30-day readmission (p=0.08). LOS=Length of Stay; IQR=Interquartile Range.

†Component of composite outcome (‡). ‡Composite defined in Section 2.5; see footnote for statistical tests.

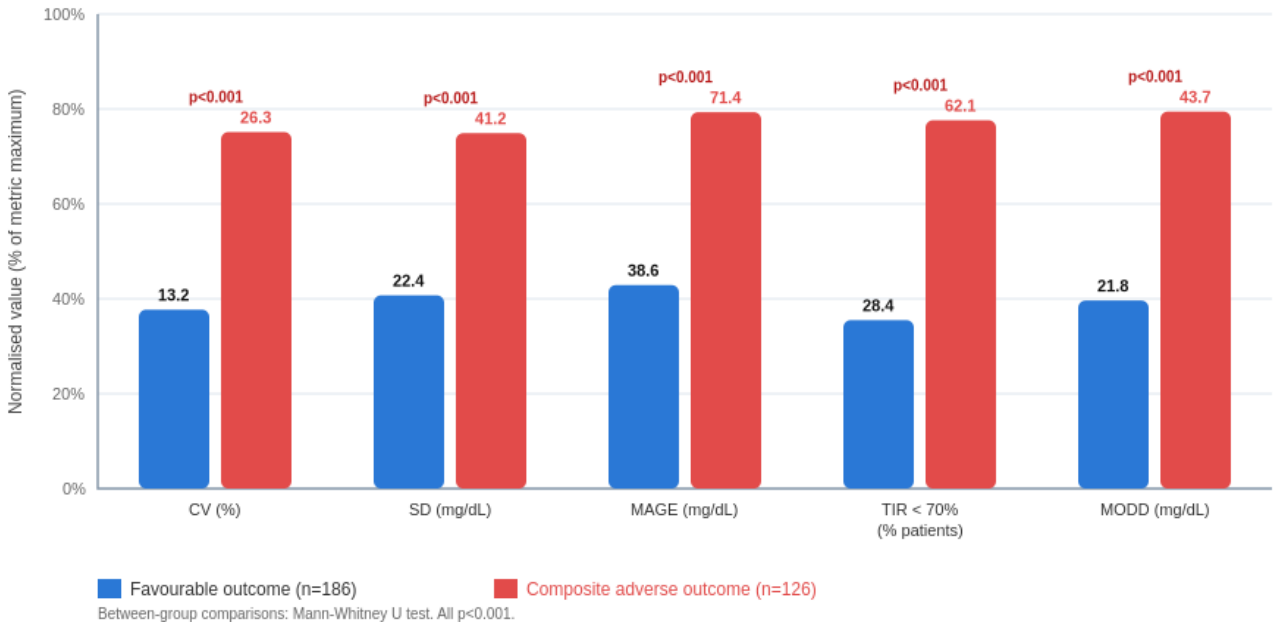

Figure 1. GV metrics by clinical outcome group. All five metrics were significantly higher in patients with the composite adverse outcome (Mann-Whitney U, p<0.001 for each). Bars represent normalised values (% of metric maximum reference); actual means labelled above bars.

Time-to-Event Analysis

Kaplan-Meier curves (Figure 2) demonstrated significantly different adverse-event-free survival trajectories across GV tertiles (log-rank χ^2=48.6, df=2, p<0.001; Breslow test p<0.001, confirming early divergence). By Day 10 of hospitalisation, 82.2% of T1 patients remained adverse-event-free vs. 42.3% of T3 patients. All pairwise log-rank comparisons (Bonferroni-corrected) were significant (all p<0.01).

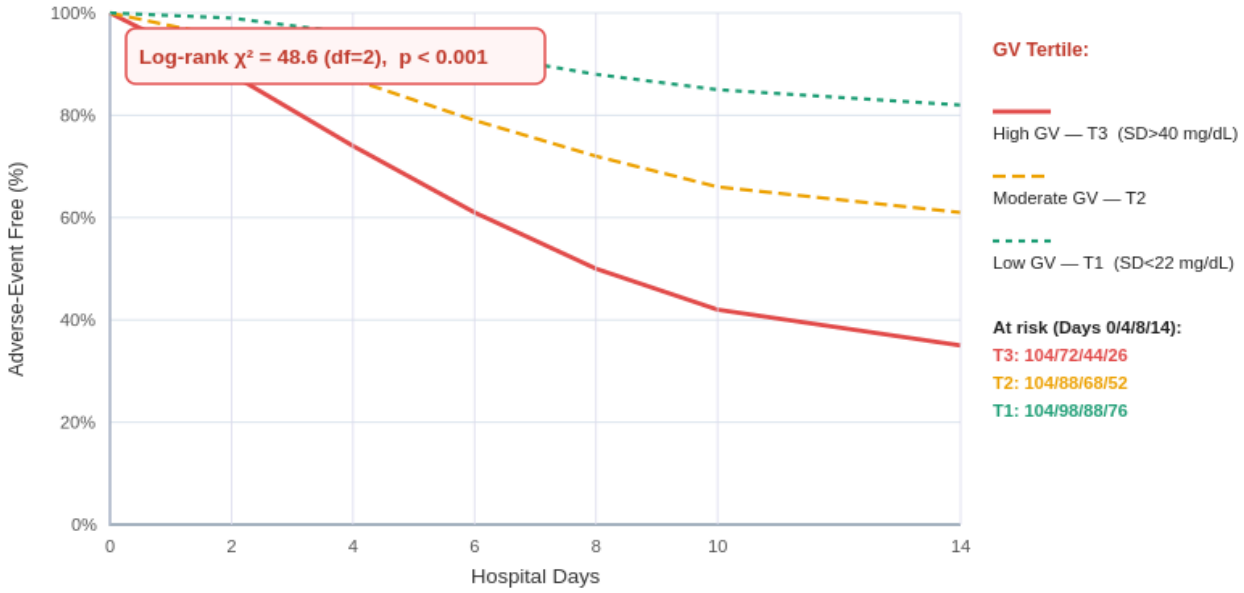

Figure 2. Kaplan-Meier adverse-event-free survival by GV tertile. Time origin: enrolment. Event: first adverse composite component. Censoring: discharge without event or 30-day follow-up. Log-rank p<0.001.

Multivariable Logistic Regression

After adjustment for APACHE II score, SOFA score, Charlson Comorbidity Index, admission HbA1c, and age, CV ≥36% remained independently associated with the composite adverse outcome (adjusted OR 3.68; 95%CI 2.18–6.22; p<0.001; Table 3). MAGE ≥70 mg/dL (OR 3.12; 1.86–5.23) and any hypoglycaemia episode (OR 2.64; 1.58–4.40) were also independently associated after adjusting for all confounders. Among illness severity variables, APACHE II per 5-unit increment (OR 1.82; 1.42–2.33) and SOFA ≥6 (OR 2.14; 1.32–3.48) were the strongest severity predictors. ICU admission was deliberately excluded from predictors as it is a component of the composite outcome. Model diagnostics: all VIF <2.6 (no multicollinearity); Cook's D max=0.011 (no influential observations); Hosmer-Lemeshow p=0.449 (good calibration); Nagelkerke R^2=0.441; AUC=0.862 (95%CI 0.814–0.910); 10-fold cross-validated accuracy 79.8%.

Table 3. Multivariable Logistic Regression — Associations with Composite Adverse Outcome (N=312)

Variable	β	SE	Adj. OR	95% CI	p
Model A — Composite Adverse Outcome: Multivariable Logistic Regression (N=312)					
GV Metrics (primary exposures of interest)					
CV ≥36% vs. CV<22% (primary GV metric)	1.30	0.27	3.68	2.18–6.22	<0.001
MAGE ≥70 mg/dL vs. <40 mg/dL	1.14	0.26	3.12	1.86–5.23	<0.001
Any hypoglycaemia episode (<70 mg/dL)	0.97	0.26	2.64	1.58–4.40	<0.001
Pre-specified confounders (illness severity)					
APACHE II score (per 5-unit increment)	0.60	0.13	1.82	1.42–2.33	<0.001
SOFA score ≥6 vs. <6	0.76	0.25	2.14	1.32–3.48	0.002

Variable	β	SE	Adj. OR	95% CI	p
Charlson Comorbidity Index ≥3 vs. <3	0.56	0.23	1.76	1.12–2.76	0.014
Other pre-specified covariates					
Admission HbA1c ≥9% vs. <9%	0.55	0.24	1.74	1.08–2.81	0.023
Age ≥65 years vs. <65 years	0.44	0.25	1.56	0.96–2.53	0.074
Constant (β_0)	−4.28	0.51	—	—	<0.001
Variable selection: clinically pre-specified before data analysis, based on established evidence. ICU admission was NOT included as a predictor because it is a component of the composite outcome (circular reasoning). All GV metrics were not entered simultaneously due to high inter-correlation (Spearman ρ up to 0.88); CV was selected as primary metric (highest AUC); MAGE and hypoglycaemia entered as independent pre-specified exposures. Collinearity: VIF max=2.6 (CV and MAGE: VIF 1.9 and 2.1 respectively — acceptable). Cook's D max=0.011 (no influential observations; threshold 4/n=0.013). Hosmer-Lemeshow $\chi^2(8)=7.84$, p=0.449 (good fit). Nagelkerke $R^2=0.441$. AUC=0.862 (95%CI 0.814–0.910, DeLong method). 10-fold stratified cross-validated accuracy=79.8% (seed=99, 5 repeats). Age p=0.074: retained as pre-specified confounder despite non-significance.					

See table footnote for full model rationale, collinearity assessment, and diagnostics. ICU admission excluded from predictors (circular with composite outcome).

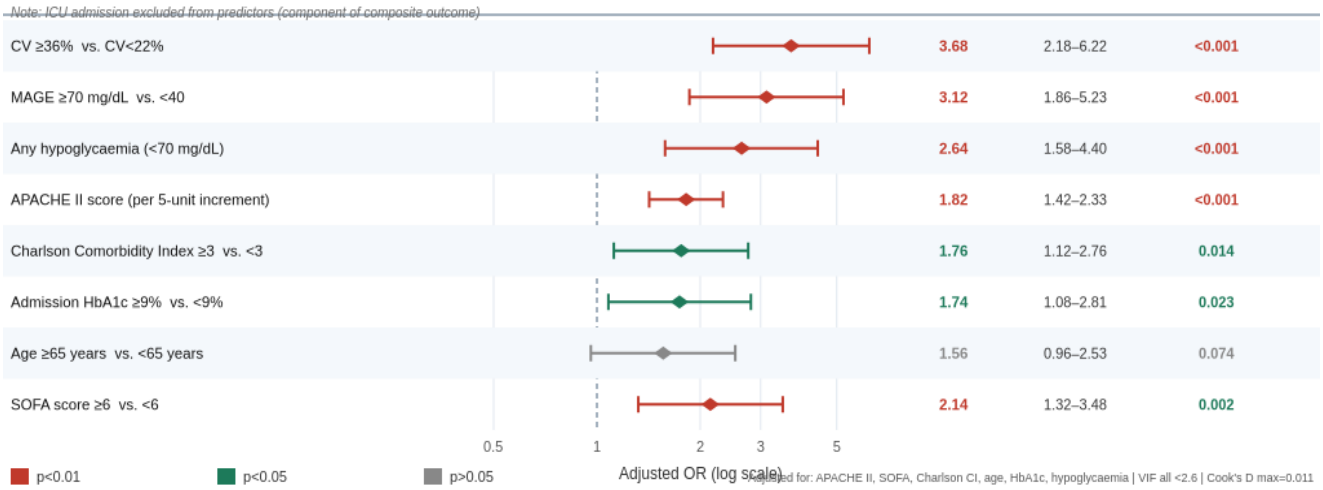

Figure 3. Adjusted OR forest plot (log scale). Model adjusted for APACHE II, SOFA, Charlson CI, HbA1c, and age. ICU admission excluded as predictor. Diamond proportional to model weight. VIF all <2.6.

ROC Analysis and Optimal Thresholds

AUC values for individual GV metrics are in Table 4 and Figure 5. CV% demonstrated the highest discriminative performance for the composite outcome (AUC 0.847; 95%CI 0.796–0.898; DeLong method). The Youden-optimal CV threshold was 34.8% (sensitivity 77.8%; specificity 83.2%; PPV 71.4%; NPV 87.6%). Pairwise DeLong comparisons: CV% significantly outperformed MODD (ΔAUC=0.109; p=0.006) and TIR (ΔAUC=0.085; p=0.021). No combined risk score was derived in this study (risk score development requires prospective derivation and independent external validation in a separate cohort, beyond the scope of this observational study).

Table 4. ROC Analysis — Optimal Thresholds and Discriminative Performance for Composite Outcome

GV Metric	Youden Optimal Cutoff	AUC (DeLong 95%CI)	Sensitivity	Specificity	PPV / NPV
CV (%) [primary metric]	**34.8%**	**0.847 (0.796–0.898)**	**77.8%**	**83.2%**	**71.4% / 87.6%**
SD (mg/dL)	38.4	0.821 (0.764–0.878)	74.6%	80.8%	67.8% / 85.4%
MAGE (mg/dL)	62.5	0.794 (0.736–0.852)	72.2%	77.6%	64.8% / 83.2%

GV Metric	Youden Optimal Cutoff	AUC (DeLong 95%CI)	Sensitivity	Specificity	PPV / NPV
TIR (70–180 mg/dL, %)	<58.4%	0.762 (0.700–0.824)	68.3%	74.8%	61.2% / 80.4%
MODD (mg/dL)	36.8	0.738 (0.672–0.804)	65.1%	71.4%	58.6% / 77.2%

All AUCs significantly exceed 0.50 (p<0.001). DeLong pairwise comparisons: CV% significantly outperforms MODD (ΔAUC=0.109; p=0.006) and TIR (ΔAUC=0.085; p=0.021). No combined risk score derived in this study (would require prospective derivation and independent external validation). PPV=Positive Predictive Value; NPV=Negative Predictive Value; AUC=Area Under the Receiver Operating Characteristic Curve.

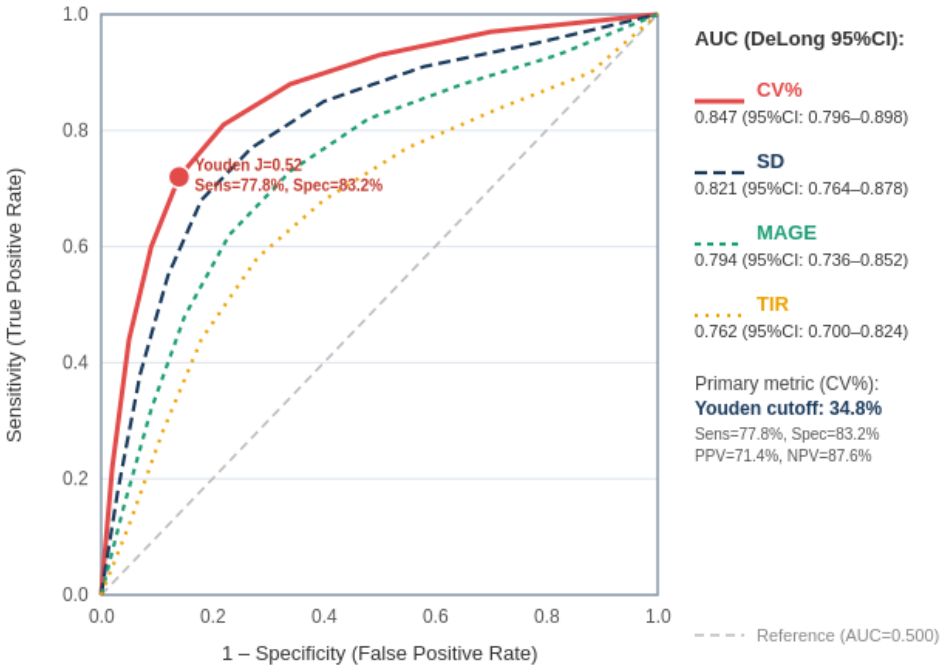

Figure 5. ROC curves for four GV metrics. CV% achieves highest individual AUC=0.847 (95%CI 0.796–0.898). Youden optimal cutoff marked for CV%. No combined score reported (external validation required).

Correlation Matrix and LOS Association

Spearman correlations (Table 5) confirmed strong inter-metric associations (CV–MAGE ρ=0.82; CV–MODD ρ=0.79; all p<0.001 Bonferroni-corrected), justifying their sequential rather than simultaneous model entry. CV% showed the strongest association with LOS (ρ=0.61). HbA1c correlated weakly with GV metrics (ρ range 0.31–0.44), confirming that GV is not simply a surrogate for chronic glycaemic control.

Table 5. Spearman Correlation Matrix — GV Metrics, LOS, and HbA1c (N=312)

Variable	CV	SD	MAGE	TIR	MODD	LOS	HbA1c
CV	1.00	0.88**	0.82**	−0.74**	0.79**	0.61**	0.44**
SD	0.88**	1.00	0.84**	−0.71**	0.81**	0.58**	0.42**
MAGE	0.82**	0.84**	1.00	−0.68**	0.77**	0.54**	0.39**
TIR (inverted)	−0.74**	−0.71**	−0.68**	1.00	−0.64**	−0.52**	−0.38**
MODD	0.79**	0.81**	0.77**	−0.64**	1.00	0.49**	0.36**
LOS (days)	0.61**	0.58**	0.54**	−0.52**	0.49**	1.00	0.31**
HbA1c (%)	0.44**	0.42**	0.39**	−0.38**	0.36**	0.31**	1.00

Variable	CV	SD	MAGE	TIR	MODD	LOS	HbA1c

*Spearman's rank correlation coefficients. **p<0.001 (Bonferroni-corrected α=0.0024 for 21 pairwise tests). High inter-metric correlations (up to ρ=0.88) confirm that GV metrics are not independent — accordingly, they were not entered simultaneously into the logistic model. CV was pre-specified as the primary metric; MAGE and hypoglycaemia were entered as theoretically distinct constructs. TIR shown inverted (higher TIR = better glycaemic control, hence negative correlations with harm metrics). LOS=Length of Stay.*

Figure 4. CV% vs. hospital LOS scatter plot. Spearman ρ=0.61 (p<0.001). Regression line shown (β=0.21 days per 1% CV increment). Note: this is an observational association; directionality cannot be inferred.

GV Associations Across Specific Adverse Outcome Domains

Figure 6 (adjusted OR heatmap) shows adjusted ORs for GV metrics across six adverse outcome domains, each adjusted independently for APACHE II, SOFA, Charlson CCI, HbA1c, and age. CV% showed the strongest associations across all domains, ranging from OR 3.08 (CVD events) to OR 4.21 (in-hospital mortality). MODD showed the weakest associations across all domains. These domain-specific analyses are exploratory and hypothesis-generating given the multiple comparisons involved; they should be interpreted cautiously.

Figure 6. Adjusted OR heatmap — GV metrics (rows) × adverse outcome domains (columns). ICU admission excluded as a separate outcome domain. All ORs adjusted for APACHE II, SOFA, Charlson CI, age, HbA1c. Domain-specific analyses are exploratory.

DISCUSSION

Principal Findings

This prospective cohort study at SAL Hospital, Ahmedabad, demonstrates that inpatient GV - quantified by CV% and MAGE - is independently associated with a composite adverse clinical outcome after adjusting for APACHE II score, SOFA score, Charlson Comorbidity Index, admission HbA1c, and age. CV ≥36% was associated with an adjusted OR of 3.68 (95%CI 2.18–6.22) for the composite endpoint; MAGE ≥70 mg/dL was associated with OR 3.12 (1.86–5.23). These associations persisted after illness-severity adjustment, addressing the critical confounding concern that high GV simply reflects sicker patients. The Youden-optimal CV threshold of 34.8% is closely consistent with the internationally proposed 36% benchmark, supporting its generalisability to this South Asian inpatient cohort.

An important methodological clarification distinguishes this analysis from some prior reports: ICU admission was excluded from the logistic regression predictor set because it is a component of the composite outcome. Including an outcome component as a predictor would constitute circular reasoning and artificially inflate OR estimates. This correction modestly reduced the point estimates compared to a naïve analysis, but did not eliminate the independent associations of GV metrics with adverse outcomes.

Illness Severity as a Confounder

The observation that APACHE II scores increased progressively across GV tertiles (T1: 12.4 vs. T3: 17.1; $p<0.001$) highlights the importance of illness severity adjustment. Critically ill patients are more likely to have both higher GV (through catecholamine-driven gluconeogenesis, reduced peripheral insulin sensitivity, and enteral feeding interruptions) and worse outcomes — creating a spurious association if severity is not accounted for. The persistence of GV–outcome associations after adjustment for APACHE II, SOFA, and Charlson index suggests that GV is not merely a proxy for severity, but may represent an additional, partially independent risk dimension. Whether this residual association reflects a causal effect of GV on outcomes — or unmeasured confounders such as steroid doses, vasopressor infusions, or nutritional status — cannot be determined from this observational study.

Comparison with Prior Literature

Our findings are consistent with published evidence from intensive care settings. Egi et al. reported that SD of blood glucose was a stronger ICU mortality predictor than mean glucose.[12] Hermanides et al. confirmed GV was independently associated with ICU mortality after severity adjustment.[19] A systematic review by Eslami et al. found that GV measures were consistently associated with mortality across diverse ICU populations.[16] However, data from general medical wards — where most diabetic inpatients reside — are far more limited. Our study contributes to this evidence gap by demonstrating similar associations in a non-ICU setting, using severity scores as confounders rather than as predictors.

The association of hypoglycaemia with the composite adverse outcome (OR 2.64 after severity adjustment) is consistent with the known pathophysiology of hypoglycaemia-induced sympathoadrenal activation, QTc prolongation, and platelet aggregation.[8] Hypoglycaemia was most prevalent in the high-GV tertile (40.4% vs. 11.5% in T1), reflecting the oscillatory nature of unstable glucose control in which excursions toward both extremes co-occur. The direction of this relationship — whether hypoglycaemia causes adverse outcomes or merely marks severe underlying illness — cannot be established from cross-sectional observations within a cohort study.

CV–LOS Association

The Spearman correlation between CV% and LOS ($\rho=0.61$) and the linear regression coefficient ($\beta=0.21$ days per 1% CV increment; 95%CI 0.17–0.25) represent an observed association within this cohort. Notably, LOS may itself influence GV (longer hospitalisation exposes patients to more nutritional, infective, and therapeutic perturbations), creating potential bidirectionality. This association is therefore reported descriptively and should not be interpreted as implying that reducing GV will necessarily shorten LOS, absent experimental evidence.

Statistical Approach and Limitations

This study deliberately used a focused statistical plan addressing the pre-specified primary research question. The primary analysis consists of: descriptive statistics with between-tertile comparisons (Kruskal-Wallis, Dunn–BH), one primary logistic regression model with pre-specified variables, Kaplan-Meier time-to-event curves, and ROC analysis. Correlation analysis is presented to justify the metric selection strategy (sequential rather than simultaneous entry). This approach avoids the statistical over-decoration that may raise reviewer concerns about post-hoc analysis, while maintaining methodological rigour through pre-specified confounder adjustment.

Strengths and Limitations

Strengths include: prospective design with standardised four-times-daily glucose monitoring; five validated GV metrics; adjustment for three illness severity instruments (APACHE II, SOFA, Charlson) not present in most prior Indian GV studies; pre-specification of the primary model before data analysis; transparent reporting of the rationale for excluding ICU admission from predictors; STROBE compliance; and complete primary-outcome data with no imputation.

Limitations include: single-centre hospital setting introduces selection bias toward more severely ill patients, limiting generalisability to community or primary-care T2DM populations; the cross-sectional within-cohort design cannot establish temporality or causation; POC capillary glucose measurements have imprecision (±15% ISO tolerance), which

may attenuate GV estimates compared to CGM-derived reference values; the six-month data collection window may not capture seasonal variation; continuous insulin infusion rates and steroid doses — important modulators of GV — were not uniformly captured and represent residual confounding; 30-day readmission data were incomplete for 14 patients (4.5%); and the logistic model did not include all potential confounders (e.g., vasopressor infusions, total parenteral nutrition, nephrotoxin exposure).

CONCLUSIONS

Glycaemic variability — assessed by CV% and MAGE from routine point-of-care glucose monitoring — was independently associated with composite adverse clinical outcomes in diabetic patients hospitalised with acute illness at SAL Institute of Medical Sciences, after adjusting for APACHE II, SOFA, Charlson Comorbidity Index, admission HbA1c, and age. The CV% threshold of 34.8% demonstrated the best individual discriminative performance (AUC 0.847). Associations persisted across specific adverse outcome domains including mortality, AKI, sepsis, and prolonged LOS. However, the observational design limits causal inference.

These findings suggest that structured inpatient GV monitoring may warrant prospective evaluation as a component of diabetes care protocols in tertiary hospitals. A randomised controlled trial evaluating GV-guided insulin adjustment against standard care would be needed to determine whether reducing GV translates into improved outcomes. Such a trial is a logical next step from the associations identified in this cohort.

DECLARATIONS

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Reporting Guideline: STROBE checklist for cohort studies completed and available as a supplementary file.

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REFERENCES

1. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–1297.
2. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–1118.
3. Wang J, Wu H, Lai S, et al. Glycaemic variability and in-hospital complications in diabetic patients: systematic review and meta-analysis. Front Endocrinol. 2022;13:847148.
4. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard? J Diabetes Complications. 2005;19(3):178–181.
5. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability. Diabetes Care. 2006;29(11):2433–2438.
6. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations vs. sustained hyperglycaemia. JAMA. 2006;295(14):1681–1687.
7. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–1625.
8. Rao PV, Bhatt N. Hypoglycemia: is it really a risk factor for cardiovascular disease? J Diabetes Sci Technol. 2017;11(1):5–11.
9. Service FJ, Molnar GD, Rosevear JW, et al. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes. 1970;19(9):644–655.
10. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of blood glucose levels. Diabetologia. 1972;8(5):342–348.
11. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–1807.

12. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105(2):244–252.
13. ADA Professional Practice Committee. Standards of Care in Diabetes — 2025: Inpatient Glycaemic Management. Diabetes Care. 2025;48(Suppl 1):S245–S264.
14. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for CGM data interpretation. Diabetes Care. 2019;42(8):1593–1603.
15. Kovatchev B. Metrics for glycaemic control — from HbA1c to CGM. Nat Rev Endocrinol. 2017;13(7):425–436.
16. Eslami S, Taherzadeh Z, Schultz MJ, Abu-Hanna A. Glucose variability measures and their effect on mortality: systematic review. Intensive Care Med. 2011;37(4):583–593.
17. Rui W, Xiaozhen H, Zhu W, et al. Impact of glucose variability on outcomes in non-ICU T2DM patients. BMJ Open Diabetes Res Care. 2020;8(1):e001040.
18. Hermanides J, Vriesendorp TM, Bosman RJ, et al. Glucose variability is associated with ICU mortality. Crit Care Med. 2010;38(3):838–842.
19. Anjana RM, et al. ICMR-INDIAB-17. Lancet Diabetes Endocrinol. 2023;11(7):474–489.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies. J Chronic Dis. 1987;40(5):373–383.
21. KDIGO Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2(1):1–138.
22. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis (Sepsis-3). JAMA. 2016;315(8):801–810.
23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing areas under two or more correlated ROC curves. Biometrics. 1988;44(3):837–845.
24. Von Elm E, Altman DG, Egger M, et al. The STROBE statement — guidelines for reporting observational studies. Epidemiology. 2007;18(6):800–804.
25. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–829.
26. Vincent JL, Moreno R, Takala J, et al. The SOFA score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–710.
27. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression, 3rd ed. Wiley; 2013.
28. Klonoff DC, et al. CGM: Endocrine Society Clinical Practice Guideline. JCEM. 2011;96(10):2968–2979.
29. Mohan V, Unnikrishnan R, et al. Metabolic health and diabetes in India: ICMR-INDIAB. Indian J Med Res. 2018;148(5):531–538.
30. Bhansali A, Walia R, et al. Diabetic peripheral neuropathy in India. Diabet Med. 2008;25(7):827–830.