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Impact of Perioperative Glycemic Variability on Surgical Outcomes in Patients With and Without Diabetes: A Multicenter Prospective Observational Study

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Abstract

Background: Perioperative hyperglycemia is associated with postoperative morbidity, but a single glucose measurement may not capture the physiological instability represented by repeated fluctuations. Glycemic variability may therefore provide prognostic information beyond diabetes status and mean glucose concentration. This multicenter prospective observational study evaluated the association between perioperative glycemic variability and 30-day surgical outcomes in patients with and without diabetes.

Methods: We analyzed 360 adults undergoing major non-cardiac surgery at Gujranwala Teaching Hospital and Mayo Hospital. Diabetes was defined as a documented diagnosis or glycated hemoglobin ⩾6.5%. A minimum of six glucose values obtained from the preoperative period through 72 hours after surgery were required to calculate glycemic variability as the coefficient of variation (CV = standard deviation/mean glucose × 100). High variability was defined as the upper cohort tertile (CV ⩾17.5%). The primary outcome was a composite of any 30-day postoperative adverse event: surgical-site infection, wound complication, pulmonary complication, acute kidney injury, sepsis, cardiac event, venous thromboembolism, ileus, anastomotic leak, reoperation, or death. Secondary outcomes were Clavien-Dindo grade III or higher complications, intensive care unit admission, readmission, and length of stay. Multivariable logistic regression adjusted for age, American Society of Anesthesiologists (ASA) class, diabetes status, surgical urgency, operative duration, and intraoperative transfusion.

Results: Of 360 patients, 109 (30.3%) had diabetes and 120 (33.3%) had high glycemic variability. At least one adverse outcome occurred in 138 patients (38.3%). The composite outcome occurred in 62.5% of patients with high variability compared with 26.3% of those with lower variability ($p < 0.001$). Among patients without diabetes, event rates were 50.9% with high variability and 23.7% with lower variability; corresponding rates among patients with diabetes were 73.0% and 37.0%, respectively. High glycemic variability remained independently associated with the composite outcome (adjusted odds ratio (aOR): 2.44; 95% CI: 1.42-4.19; $p = 0.001$). This association persisted in a sensitivity analysis additionally adjusting for mean perioperative glucose ⩾180 mg/dL and intraoperative hypotension (aOR: 2.33; $p = 0.003$). Diabetes (aOR: 2.49; 95% CI: 1.44-4.31), emergency surgery (aOR: 2.68; 95% CI: 1.56-4.58), ASA class III or higher (aOR: 2.00; 95% CI: 1.07-3.75), operative duration >180 minutes (aOR: 1.66; 95% CI: 1.01-2.72), and intraoperative transfusion (aOR: 1.84; 95% CI: 1.05-3.24) were also independently associated with the composite outcome. The diabetes-by-variability interaction was not statistically significant ($p = 0.703$).

Conclusions: Perioperative glycemic variability was independently associated with postoperative morbidity in patients with and without diabetes, with the greatest absolute risk observed among patients with both diabetes and high glycemic variability. However, reverse causation cannot be excluded, as complications arising during the 72-hour glucose-monitoring window may themselves increase glycemic variability. Prospective studies incorporating time-resolved analyses are needed to clarify the temporal relationship and determine whether improving glucose stability reduces postoperative complications.

Categories: General Surgery, Endocrinology/Diabetes/Metabolism, Anesthesiology
Keywords: coefficient of variation, diabetes mellitus, glucose monitoring, glycemic variability, perioperative hyperglycemia, postoperative complications, surgical outcomes

Introduction

Dysglycemia is common during the perioperative period. Surgical stress activates counter-regulatory hormones and inflammatory pathways, increases hepatic glucose production, and promotes peripheral

insulin resistance. Fasting, dextrose-containing fluids, nutrition, medications, and interruptions in usual diabetes therapy can further alter glucose homeostasis [1-3]. These effects occur in patients with established diabetes and in individuals without a prior diabetes diagnosis. Perioperative hyperglycemia has consequently been associated with surgical-site infection, delayed wound healing, acute kidney injury, cardiovascular events, prolonged hospitalization, and mortality across diverse surgical populations [3,4].

Most perioperative protocols emphasize absolute glucose thresholds and avoidance of severe hyperglycemia or hypoglycemia. Contemporary guidance generally favors moderate glucose targets rather than intensive normalization because aggressive insulin therapy can provoke hypoglycemia without consistently improving outcomes [1,2]. However, mean glucose concentration or a single peak value does not describe the temporal instability of glucose exposure. Two patients may have the same mean glucose concentration while experiencing markedly different excursions. Such variability may reflect greater metabolic stress, inconsistent insulin delivery, nutritional disruption, or impaired physiological reserve.

Glycemic variability can be quantified using the standard deviation, coefficient of variation, mean amplitude of glycemic excursions, or time-derived metrics from continuous glucose monitoring [5-7]. The coefficient of variation is particularly useful because it standardizes the standard deviation to mean glucose concentration and permits comparison across patients with different average glucose levels [5]. In medical and critical-care populations, increased glycemic variability has been associated with oxidative stress, endothelial dysfunction, inflammation, and adverse outcomes [6,7]. Surgical studies have similarly reported associations between postoperative variability and infection, reoperation, length of stay, delirium, and mortality, although much of the available evidence is procedure-specific and retrospective [6-10].

The prognostic implications of perioperative dysglycemia may differ according to pre-existing diabetes status. Patients with chronic hyperglycemia may partially adapt to higher glucose concentrations, whereas acute stress hyperglycemia in a person without diabetes may indicate severe physiological stress or an unrecognized disturbance in glucose regulation. Prior work has suggested that comparable perioperative hyperglycemia may carry a greater relative risk in patients without known diabetes, even though patients with diabetes often have a higher absolute burden of dysglycemia [4]. Whether glycemic variability itself has a differential relationship with postoperative outcomes in diabetic and non-diabetic surgical patients remains incompletely characterized.

Although previous surgical studies have linked glycemic variability with postoperative complications, much of the available evidence has been retrospective or focused on specific surgical procedures, with limited prospective evaluation across multiple surgical specialties. Furthermore, the association between perioperative glycemic variability and postoperative outcomes in patients with and without diabetes, particularly after adjustment for mean glucose and established perioperative risk factors, remains insufficiently characterized. To address these gaps, this multicenter prospective observational study aimed to assess the association between high perioperative glycemic variability and a composite outcome comprising any adverse postoperative event occurring within 30 days of surgery, after adjustment for diabetes status and established perioperative risk factors. Secondary objectives were to compare individual complications, length of stay, major morbidity, readmission, and mortality between patients with and without diabetes; describe outcome rates across combined diabetes/variability strata; and assess whether diabetes modified the association between glycemic variability and postoperative outcomes.

Materials And Methods

Study design, setting, and ethics

This multicenter prospective observational cohort study was conducted at two tertiary teaching hospitals in Punjab, Pakistan (Gujranwala Teaching Hospital and Mayo Hospital). Eligible patients were enrolled between July 2025 and December 2025 and followed for 30 days after surgery. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11]. The protocol was approved by the Institutional Review Board of Gujranwala Medical College and Gujranwala Teaching Hospital (approval number: 67/GMC).

Sample-size estimation was based on the planned multivariable logistic regression analysis. Assuming a composite outcome incidence of 30-35% and a minimum of approximately 10 outcome events per candidate predictor, at least 340 participants were required to support a model containing 10-11 clinically selected variables. The final analytical cohort included 360 patients.

Participants and perioperative data collection

Adults aged 18 years or older were eligible if they underwent major non-cardiac general/abdominal, orthopedic, gynecologic, or urologic surgery under general or neuraxial anesthesia and were expected to require inpatient hospitalization for at least 48 hours. Both elective and emergency procedures were included. Major surgery was defined as a procedure requiring operating-room anesthesia, planned inpatient admission, and sufficient physiological stress to warrant serial perioperative glucose monitoring.

Patients undergoing minor or ambulatory procedures, cardiac or transplant surgery, or surgery during pregnancy were excluded. Additional exclusions were diabetic ketoacidosis or hyperosmolar hyperglycemic state at presentation, fewer than six valid perioperative glucose measurements, loss to 30-day follow-up, and repeat eligible operations during the study period; only the first eligible operation was included.

Baseline and perioperative variables included age, sex, body mass index, smoking status, American Society of Anesthesiologists (ASA) physical status class [12], relevant comorbidities, surgical specialty, urgency of surgery, operative approach, operative duration, estimated blood loss, intraoperative hypotension, intraoperative blood transfusion, postoperative nutritional route, and critical-care admission. Intraoperative hypotension was defined as a mean arterial pressure below 65 mmHg for a cumulative duration of at least 10 minutes or sustained vasopressor requirement. Intraoperative transfusion was defined as administration of at least one unit of packed red blood cells. Perioperative glucose management followed usual institutional practice and was not directed by the study team.

Perioperative glucose monitoring and exposure definitions

Diabetes mellitus was defined as a documented diagnosis of type 1 or type 2 diabetes or a preoperative glycated hemoglobin value of at least 6.5%. Patients without a known diagnosis of diabetes and with glycated hemoglobin below 6.5% were classified as not having diabetes.

Glucose measurements included a fasting or admission value, a value at induction of anesthesia, measurements at least every two hours during operations lasting more than two hours, a post-anesthesia care unit value, and measurements approximately every six hours during the first 72 postoperative hours. Eligible measurements were obtained using validated capillary point-of-care testing or arterial or venous blood samples. At least six valid readings were required for variability analysis. The requirement for at least six valid glucose measurements was applied to ensure a minimum level of sampling completeness for calculating glycemic variability, although the number and timing of available measurements could vary between participants.

For each patient, mean perioperative glucose and within-patient standard deviation were calculated from all eligible glucose readings. Glycemic variability was expressed as the coefficient of variation: CV (%) = (standard deviation of glucose ÷ mean glucose) × 100.

High glycemic variability was predefined as the upper cohort tertile; in this cohort, this corresponded to a coefficient of variation of at least 17.5%. Hyperglycemia was defined as any glucose value of at least 180 mg/dL and hypoglycemia as any value below 70 mg/dL [1,2]. Mean perioperative glucose of at least 180 mg/dL was evaluated as a secondary glycemic exposure.

Outcomes

The primary outcome was the occurrence of at least one adverse postoperative event within 30 days of surgery. The composite outcome included surgical-site infection, wound dehiscence or delayed wound healing, pulmonary complication, acute kidney injury, sepsis, clinically significant cardiac event, venous thromboembolism, prolonged postoperative ileus, anastomotic leak, unplanned reoperation, or death. The 30-day composite outcome included postoperative complications occurring during the initial 72-hour glucose-assessment period, and events were not excluded based on their timing within the follow-up period. Individual components were recorded separately, and patients could experience more than one event.

Surgical-site infection was classified as superficial incisional, deep incisional, or organ/space infection. Pulmonary complications included pneumonia, respiratory failure requiring unplanned ventilatory support, or clinically significant atelectasis requiring therapeutic intervention. Acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes criteria [13], and sepsis was defined according to Sepsis-3 principles [14]. Cardiac events included myocardial infarction, clinically significant arrhythmia requiring treatment, or new or worsening heart failure. Venous thromboembolism required imaging-confirmed deep-vein thrombosis or pulmonary embolism, while anastomotic leak required radiological, operative, or drain-based confirmation. Major morbidity was defined as Clavien-Dindo grade III or higher [15].

Secondary outcomes were individual postoperative complications, major morbidity, intensive care unit admission or escalation, unplanned reoperation, 30-day readmission, 30-day mortality, and postoperative length of stay. Follow-up was completed through inpatient review and a 30-day clinic or telephone assessment. Records were reviewed for completeness, plausible ranges, and internal consistency before analysis. Because glycemic variability was assessed over the first 72 postoperative hours, early complications could have occurred during the glucose-assessment period; therefore, temporal precedence of glycemic variability over all postoperative outcomes could not be established.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation when approximately normally

distributed and as median with interquartile range when skewed. Categorical variables were reported as frequencies and percentages. Comparisons between patients with and without diabetes used the independent-samples t-test or Mann-Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. Outcome rates were also compared between high- and lower-variability groups and across four combined strata: no diabetes/lower variability, no diabetes/high variability, diabetes/lower variability, and diabetes/high variability.

Univariable logistic regression was used to estimate crude associations with the composite outcome. Candidate covariates were selected a priori based on clinical relevance and included age over 60 years, sex, ASA class III or higher, diabetes, emergency surgery, operative approach, operative duration over 180 minutes, intraoperative hypotension, intraoperative transfusion, mean glucose of at least 180 mg/dL, high glycemic variability, and hypoglycemia.

The primary multivariable model included age over 60 years, ASA class III or higher, diabetes status, emergency surgery, operative duration over 180 minutes, intraoperative transfusion, and high glycemic variability. Variance inflation factors were assessed to identify problematic multicollinearity, with values above 5 considered potentially concerning. A prespecified diabetes-by-high-variability interaction term was included to assess effect modification. A sensitivity model additionally included mean glucose of at least 180 mg/dL and intraoperative hypotension. Adjusted associations are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). All tests were two-sided, and $p<0.05$ was considered statistically significant. All analyses were performed using Python version 3.13 (Python Software Foundation, Wilmington, Delaware, USA).

Results

Participant flow

Of 394 patients assessed for eligibility, 22 were excluded before enrollment: 12 were scheduled for minor or ambulatory procedures, six declined participation, and four had diabetic ketoacidosis, hyperosmolar hyperglycemic state, or another acute metabolic emergency. Of the 372 enrolled patients, seven had fewer than six eligible perioperative glucose measurements, and five were lost to 30-day follow-up. The final analytical cohort therefore comprised 360 patients, including 251 (69.7%) without diabetes and 109 (30.3%) with diabetes (Figure *1*).

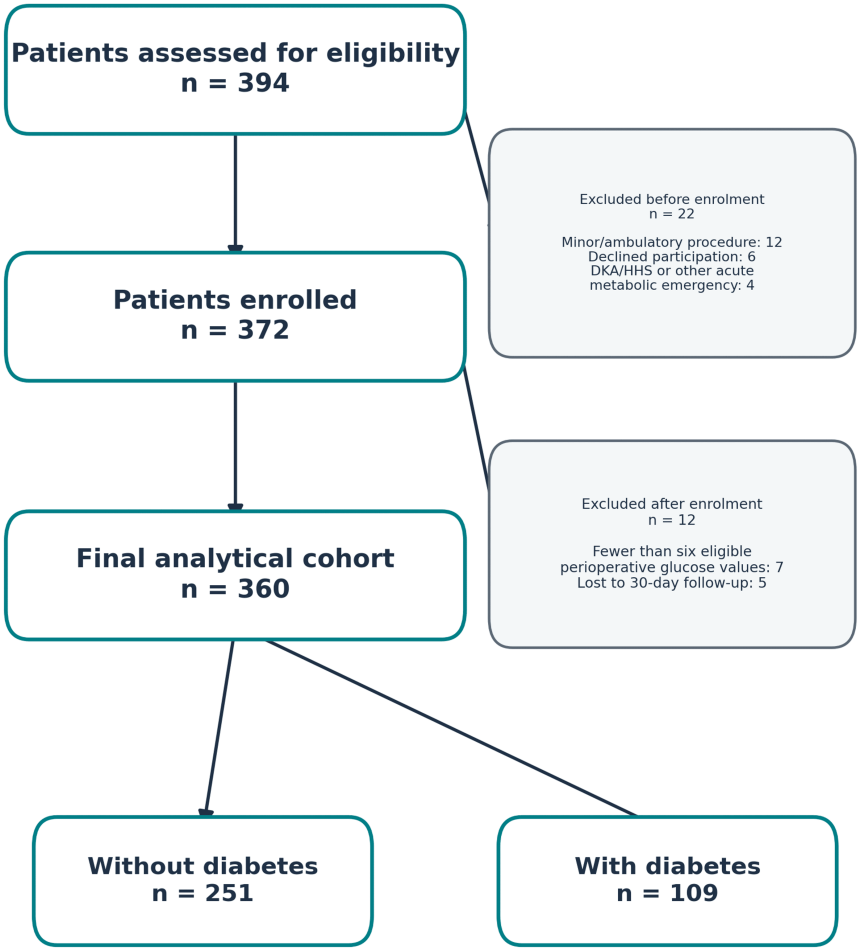


FIGURE 1: Participant flow diagram of the study cohort.

DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state

Baseline and perioperative characteristics

The mean age of the cohort was 50.4 years, and 215 patients (59.7%) were male. Compared with patients without diabetes, those with diabetes were older, more frequently had ASA class III or higher, and had higher glycated hemoglobin, mean perioperative glucose, and glucose coefficient of variation. Sex, body mass index, emergency surgery, operative approach, prolonged operative duration, intraoperative hypotension, and intraoperative transfusion did not differ significantly between groups.

High glycemic variability was present in 63 of 109 patients with diabetes (57.8%) and 57 of 251 patients without diabetes (22.7%; $p < 0.001$). Mean perioperative glucose of at least 180 mg/dL occurred in 35 patients with diabetes (32.1%) and one patient without diabetes (0.4%; $p < 0.001$). Hypoglycemia was uncommon overall but occurred more frequently in patients with diabetes than in those without diabetes (11.0% versus 3.6%; $p = 0.012$) (Table *1*).

Characteristic	Overall (n = 360)	Without diabetes (n = 251)	With diabetes (n = 109)	Test statistic	P-value
Age, years, mean ± SD	50.4 ± 15.0	48.5 ± 14.7	54.8 ± 14.7	t = 3.74	<0.001
Age >60 years	81 (22.5)	44 (17.5)	37 (33.9)	χ^2 = 10.82	0.001
Male sex	215 (59.7)	147 (58.6)	68 (62.4)	χ^2 = 0.32	0.574
Body mass index, kg/m², mean ± SD	25.2 ± 4.2	24.9 ± 4.1	25.9 ± 4.4	t = 1.95	0.052
ASA class ≥III	66 (18.3)	37 (14.7)	29 (26.6)	χ^2 = 6.38	0.012
Emergency surgery	113 (31.4)	77 (30.7)	36 (33.0)	χ^2 = 0.10	0.751
Open surgical approach	198 (55.0)	137 (54.6)	61 (56.0)	χ^2 = 0.02	0.899
Operative duration >180 minutes	155 (43.1)	111 (44.2)	44 (40.4)	χ^2 = 0.32	0.573
Intraoperative hypotension	100 (27.8)	65 (25.9)	35 (32.1)	χ^2 = 1.17	0.280
Intraoperative transfusion	84 (23.3)	55 (21.9)	29 (26.6)	χ^2 = 0.69	0.406
HbA1c, %, mean ± SD	6.1 ± 1.4	5.4 ± 0.5	7.6 ± 1.5	t = 14.96	<0.001
Mean perioperative glucose, mg/dL	139.3 ± 31.9	126.2 ± 16.7	169.4 ± 35.4	t = 12.17	<0.001
Glucose coefficient of variation, %	15.6 ± 6.3	14.2 ± 5.1	18.8 ± 7.5	t = 5.84	<0.001
High glycemic variability (CV ≥17.5%)	120 (33.3)	57 (22.7)	63 (57.8)	χ^2 = 40.46	<0.001
Mean glucose ≥180 mg/dL	36 (10.0)	1 (0.4)	35 (32.1)	χ^2 = 81.43	<0.001
Any glucose <70 mg/dL	21 (5.8)	9 (3.6)	12 (11.0)	χ^2 = 6.33	0.012

TABLE 1: Baseline, operative, and glycemic characteristics according to diabetes status.

Data are presented as n (%) unless otherwise specified. Continuous variables were compared using independent-samples t-tests and categorical variables using Pearson chi-squared tests with continuity correction. The test-statistic column reports t or χ^2, as appropriate. All p-values are two-sided.

ASA: American Society of Anesthesiologists; CV: coefficient of variation; HbA1c: glycated hemoglobin; SD: standard deviation

Postoperative outcomes by diabetes status

At least one 30-day adverse postoperative outcome occurred in 138 patients (38.3%). The composite outcome was more frequent among patients with diabetes than among those without diabetes (57.8% versus 29.9%; $p < 0.001$). Major complications, surgical-site infection, wound dehiscence or delayed healing, acute kidney injury, sepsis, anastomotic leak, unplanned reoperation, and 30-day readmission were also more frequent among patients with diabetes. Mortality occurred only in the diabetes group; however, this comparison should be interpreted cautiously because only three deaths occurred overall. Anastomotic leaks occurred in 16 patients (4.4% of the overall cohort), including seven patients without diabetes and nine patients with diabetes. These percentages were calculated using the entire study population and should not be interpreted as leak rates among patients who underwent an anastomosis.

There were no statistically significant between-group differences in pulmonary complications, cardiac complications, venous thromboembolism, prolonged postoperative ileus, or intensive care unit admission or escalation. The median postoperative length of stay was 10 days (interquartile range: 7-12 days) in patients with diabetes and six days (interquartile range: 5-9 days) in those without diabetes ($p < 0.001$) (Table *2*).

Outcome	Overall (n = 360)	Without diabetes (n = 251)	With diabetes (n = 109)	Test statistic	P-value
Any 30-day adverse outcome	138 (38.3)	75 (29.9)	63 (57.8)	$\chi^2 = 23.89$	<0.001
Major complication (Clavien-Dindo ≥III)	76 (21.1)	39 (15.5)	37 (33.9)	$\chi^2 = 14.38$	<0.001
Surgical-site infection	54 (15.0)	20 (8.0)	34 (31.2)	$\chi^2 = 30.35$	<0.001
Wound dehiscence/delayed healing	37 (10.3)	19 (7.6)	18 (16.5)	$\chi^2 = 5.66$	0.017
Pulmonary complication	29 (8.1)	16 (6.4)	13 (11.9)	$\chi^2 = 2.46$	0.117
Acute kidney injury	39 (10.8)	19 (7.6)	20 (18.3)	$\chi^2 = 8.06$	0.005
Sepsis	38 (10.6)	19 (7.6)	19 (17.4)	$\chi^2 = 6.82$	0.009
Cardiac complication	18 (5.0)	10 (4.0)	8 (7.3)	$\chi^2 = 1.16$	0.281
Venous thromboembolism	9 (2.5)	7 (2.8)	2 (1.8)	Fisher's exact test	0.729
Prolonged postoperative ileus	32 (8.9)	19 (7.6)	13 (11.9)	$\chi^2 = 1.28$	0.257
Anastomotic leak	16 (4.4)	7 (2.8)	9 (8.3)	$\chi^2 = 4.14$	0.042
Unplanned reoperation	28 (7.8)	11 (4.4)	17 (15.6)	$\chi^2 = 11.81$	<0.001
ICU admission/escalation	59 (16.4)	35 (13.9)	24 (22.0)	$\chi^2 = 3.05$	0.081
30-day readmission	43 (11.9)	18 (7.2)	25 (22.9)	$\chi^2 = 16.49$	<0.001
30-day mortality	3 (0.8)	0 (0.0)	3 (2.8)	Fisher's exact test	0.027*
Postoperative length of stay, days, median (IQR)	7 (5-11)	6 (5-9)	10 (7-12)	-	<0.001

TABLE 2: Thirty-day postoperative outcomes according to diabetes status.

Data are presented as n (%) unless otherwise specified. Categorical outcomes were compared using Pearson chi-squared tests with continuity correction; Fisher's exact tests were used when expected cell frequencies were below five. Postoperative length of stay was compared using the Mann-Whitney U test. The test-statistic column reports χ^2, U, or Fisher's exact test, as appropriate. All p-values are two-sided.

ICU: intensive care unit; IQR: interquartile range

Outcomes according to glycemic variability

The composite outcome occurred in 75 of 120 patients with high glycemic variability (62.5%) and 63 of 240 patients with lower variability (26.3%; $p < 0.001$). In unadjusted comparisons, high variability was also associated with higher rates of major complications, surgical-site infection, acute kidney injury, sepsis, unplanned reoperation, intensive care unit admission or escalation, and 30-day readmission (all $p \leq 0.002$).

Within both diabetes strata, high glycemic variability was associated with a higher composite-outcome rate. Among patients without diabetes, rates were 23.7% with lower variability and 50.9% with high variability. Among patients with diabetes, the corresponding rates were 37.0% and 73.0%, respectively. The greatest absolute event rate occurred in patients with both diabetes and high glycemic variability (Figure *2*).

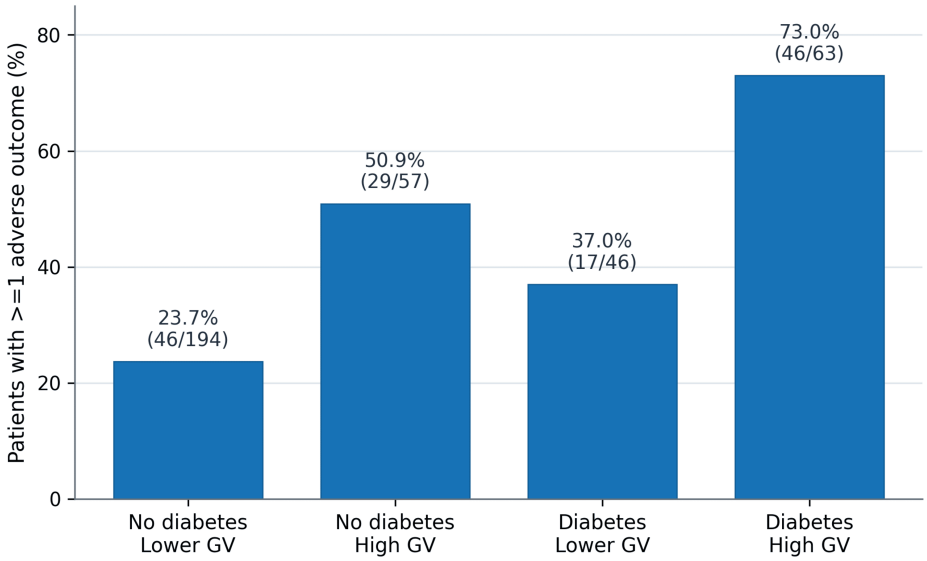


FIGURE 2: Thirty-day composite adverse-outcome rates according to diabetes status and perioperative glycemic variability.

High variability was defined as glucose CV ≥17.5%, the upper tertile of the cohort.

GV: glycemic variability; CV: coefficient of variation

Univariable analysis

On univariable logistic regression, age greater than 60 years, ASA class III or higher, diabetes, emergency surgery, operative duration greater than 180 minutes, intraoperative hypotension, intraoperative transfusion, mean perioperative glucose of at least 180 mg/dL, and high glycemic variability were associated with the composite outcome. High glycemic variability showed the largest crude association among the evaluated variables (odds ratio: 4.68; 95% CI: 2.93-7.48; $p < 0.001$). Sex, open surgical approach, and hypoglycemia were not significantly associated with the composite outcome (Table 3).

Candidate predictor	Crude OR	95% CI	P-value
Age >60 years	1.92	1.17-3.17	0.010
Male sex	1.32	0.85-2.04	0.218
ASA class ≥III	2.44	1.42-4.19	0.001
Diabetes mellitus	3.21	2.02-5.12	<0.001
Emergency surgery	3.82	2.39-6.10	<0.001
Open surgical approach	1.34	0.87-2.06	0.184
Operative duration >180 minutes	1.66	1.08-2.55	0.021
Intraoperative hypotension	2.19	1.37-3.51	0.001
Intraoperative transfusion	2.27	1.38-3.73	0.001
Mean glucose ≥180 mg/dL	4.24	2.02-8.94	<0.001
High glycemic variability	4.68	2.93-7.48	<0.001
Any glucose <70 mg/dL	0.79	0.31-2.02	0.628

TABLE 3: Univariable logistic regression for the composite 30-day adverse outcome.

ASA: American Society of Anesthesiologists; CI: confidence interval; OR: odds ratio

Multivariable analysis

In the primary multivariable model, high glycemic variability remained independently associated with the composite outcome (aOR: 2.44; 95% CI: 1.42-4.19; p = 0.001). Diabetes, emergency surgery, ASA class III or higher, operative duration greater than 180 minutes, and intraoperative transfusion were also independently associated with the outcome. Age greater than 60 years was not statistically significant after adjustment. Variance inflation factors were below 2.5 for all covariates, indicating no important multicollinearity (Table 4).

Independent predictor	Adjusted OR	95% CI	P-value
Age >60 years	1.28	0.71-2.32	0.416
ASA class ≥III	2.00	1.07-3.75	0.030
Diabetes mellitus	2.49	1.44-4.31	0.001
Emergency surgery	2.68	1.56-4.58	<0.001
Operative duration >180 minutes	1.66	1.01-2.72	0.044
Intraoperative transfusion	1.84	1.05-3.24	0.034
High glycemic variability	2.44	1.42-4.19	0.001

TABLE 4: Multivariable logistic regression for the composite 30-day adverse outcome.

The model contained 138 outcome events for seven predictors.

ASA: American Society of Anesthesiologists; CI: confidence interval; OR: odds ratio

There was no statistical evidence that diabetes status modified the association between high glycemic variability and the composite outcome (p for interaction = 0.703). In the prespecified sensitivity analysis, additionally including intraoperative hypotension and mean perioperative glucose of at least 180 mg/dL, the association between high glycemic variability and the composite outcome remained statistically significant (aOR: 2.33; p = 0.003).

Discussion

Principal findings

In this multicenter prospective observational cohort, high perioperative glycemic variability was independently associated with 30-day postoperative morbidity. The composite outcome occurred in 62.5% of patients with high glycemic variability compared with 26.3% of those with lower variability. After adjustment for age, ASA class, diabetes status, emergency surgery, operative duration, and intraoperative transfusion, high variability remained associated with adverse outcomes (aOR: 2.44; 95% CI: 1.42-4.19; p = 0.001). This association also remained statistically significant in the sensitivity analysis incorporating mean perioperative glucose of at least 180 mg/dL and intraoperative hypotension.

The highest absolute event rate occurred among patients with both diabetes and high glycemic variability (73.0%). However, patients without diabetes who had high variability also had a substantial event rate (50.9%), exceeding that of patients with diabetes and lower variability (37.0%). The diabetes-by-variability interaction was not statistically significant (p = 0.703); however, this finding should not be interpreted as evidence of equivalent associations across diabetes groups, as the study may have had limited statistical power to detect effect modification. Although higher glycemic variability was associated with increased postoperative risk in both groups, the magnitude of this association may differ and warrants further investigation in larger cohorts. In particular, glucose fluctuations in patients without known diabetes should not be dismissed as incidental stress hyperglycemia.

Relationship to previous evidence

Our findings are consistent with evidence linking perioperative hyperglycemia to adverse surgical outcomes in patients with and without diabetes. Kotagal et al. reported a dose-dependent association between perioperative hyperglycemia and postoperative adverse events, with an especially important relative risk signal among patients without a documented diabetes diagnosis [4]. Acute dysglycemia in a patient without diabetes may reflect severe physiological stress, unrecognized diabetes, or impaired metabolic reserve, whereas diabetes also represents a chronic burden of vascular, renal, and metabolic comorbidity.

Growing evidence suggests that glucose variability may provide clinically relevant information beyond isolated glucose thresholds. In orthopedic surgery, increased postoperative glucose variability has been associated with infection, prolonged hospitalization, reoperation, and mortality [6,7]. Similar associations between perioperative glycemic disturbance or variability and postoperative complications have been reported in non-cardiac surgery, patients with type 2 diabetes, and lumbar spine surgery [8-10]. In cardiac surgery, early postoperative glucose variability has also been associated with increased serum endocan, a marker of endothelial injury, supporting a possible biological link between glucose instability and vascular dysfunction [16].

Potential mechanisms

The association between glycemic variability and postoperative complications is biologically plausible but should not be interpreted as proof of causation. Rapid glucose excursions may promote oxidative stress, endothelial dysfunction, inflammatory signaling, and impaired microvascular perfusion. Hyperglycemia can adversely affect neutrophil chemotaxis, phagocytosis, collagen synthesis, and wound healing, while hypoglycemic episodes may trigger catecholamine release and cardiovascular stress [3]. The observed relationship between postoperative glucose variability and serum endocan in cardiac surgical patients further supports endothelial injury as one possible pathway [16].

Variability may also function as a marker of illness severity and treatment complexity. Emergency surgery, infection, hemodynamic instability, vasopressor exposure, steroid administration, interruption of nutrition, dextrose administration, and inconsistent insulin delivery can all increase glucose fluctuations while independently worsening postoperative outcomes. Although multivariable adjustment reduced the likelihood that the findings were explained solely by measured confounders, residual confounding remains possible.

Clinical implications

Current perioperative guidance appropriately prioritizes avoidance of severe hyperglycemia and hypoglycemia, using moderate glucose targets rather than indiscriminate intensive normalization [1,2]. Our findings do not support chasing every individual glucose fluctuation with aggressive insulin therapy. Rather, repeated perioperative glucose measurements should be interpreted as a trajectory. Unexpected or persistent variability should prompt assessment for potentially reversible contributors, including occult infection, inadequate perfusion, inconsistent nutrition, medication interruption, steroid exposure, poorly timed insulin, or measurement error.

Although glycemic variability was associated with postoperative complications, its incremental predictive value beyond established perioperative risk factors was not formally evaluated. Therefore, the clinical utility of incorporating glycemic variability into routine perioperative risk assessment remains uncertain and

requires prospective validation before implementation. Interventions aimed at improving nutritional consistency and insulin delivery may be reasonable areas for study; however, evidence remains insufficient to conclude that preoperative carbohydrate loading reduces glycemic variability or improves surgical outcomes [17]. Any variability-focused strategy should complement, rather than replace, established surgical-site-infection prevention measures and safe perioperative glycemic-control protocols for patients with and without diabetes [18].

Strengths and limitations

This study included patients with and without diabetes undergoing major surgery across two tertiary hospitals and used serial glucose measurements spanning the preoperative, intraoperative, and early postoperative periods. Diabetes classification incorporated both documented diagnosis and glycated hemoglobin, reducing misclassification of previously unrecognized chronic hyperglycemia. The study also assessed a clinically broad 30-day outcome, reported individual complications, adjusted for important perioperative risk factors, and evaluated whether diabetes modified the association between glycemic variability and postoperative morbidity.

Several limitations should be considered. First, the observational design precludes causal inference. Important treatment and severity variables, including insulin dose and timing, dextrose exposure, nutritional interruptions, steroid use, and evolving organ dysfunction, may have influenced both glycemic variability and postoperative outcomes. Furthermore, reverse causation cannot be excluded, as glycemic variability was calculated using measurements obtained through the first 72 postoperative hours, during which complications may already have developed. Early postoperative events, such as infection, sepsis, or acute organ dysfunction, could themselves increase glucose fluctuations through physiological stress, inflammatory responses, or changes in treatment. Therefore, the temporal relationship between glycemic variability and postoperative complications cannot be definitively established. Future studies incorporating time-stamped complication onset and glucose measurements preceding adverse events may help clarify this relationship. Second, intermittent glucose sampling may miss short-lived excursions, and coefficient-of-variation estimates are influenced by measurement frequency. Furthermore, capillary point-of-care glucose measurements may be less accurate in patients with impaired peripheral perfusion, particularly during hypotension, hypothermia, or vasopressor use, potentially introducing measurement error into glycemic variability estimates. Third, the coefficient of variation threshold of 17.5% was based on the upper cohort tertile and may not be directly generalizable to other surgical populations with different baseline metabolic profiles. Fourth, the composite outcome included events of unequal clinical importance, while several individual outcomes were too infrequent for stable independent analysis. Although mean perioperative glucose was incorporated into the sensitivity analysis using a threshold of ⩾180 mg/dL, it was not evaluated as a continuous covariate, and residual confounding by average glucose concentration cannot be excluded. Additionally, differences in surgical specialty and study center may have influenced the observed associations, as these factors were not included in the adjusted models. The lack of anastomosis-specific denominators and detailed numerical stratification of individual complications by glycemic variability limits the interpretation of these secondary outcomes.

Future studies should use larger multicenter cohorts with standardized glucose-measurement protocols, detailed real-time capture of insulin, dextrose, nutrition, and steroid exposure, and adjustment for procedure-level and hospital-level effects. Continuous glucose monitoring may help determine whether higher-resolution metrics such as time in range, hyperglycemic burden, and hypoglycemic burden provide greater prognostic value than intermittent measurements alone. Ultimately, randomized studies are needed to establish whether interventions that improve perioperative glucose stability can reduce complications without increasing hypoglycemia.

Conclusions

In this multicenter prospective observational cohort, high perioperative glycemic variability was independently associated with 30-day adverse postoperative outcomes in patients with and without diabetes. Although higher absolute event rates were observed among patients with diabetes, the nonsignificant diabetes-by-variability interaction does not establish equivalent associations across diabetes groups. The incremental predictive value and clinical utility of glycemic variability beyond established perioperative risk factors remain uncertain. Given the observational design and potential for reverse causation, these findings should not be interpreted as demonstrating that reducing glycemic variability would improve postoperative outcomes. Further prospective studies are warranted to clarify its prognostic value and determine whether interventions targeting glucose stability can safely improve surgical outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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