Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The Association Between Glycemic Variability and Infectious Complications Following Upfront Surgery for Early-Stage Gastric Cancer

Canbert Celik

canbertcelik@gmail.com

University of Health Sciences, Ankara Bilkent City Hospital

Yasin Orhan Erkus

Ministry of Health, Ankara Bilkent City Hospital

Ali Sapmaz

University of Health Sciences, Ankara Bilkent City Hospital

Serhan Yilmaz

University of Health Sciences, Ankara Bilkent City Hospital

Research Article

Keywords: Early stage gastric cancer, Glycemic variability, Postoperative complications

Posted Date: September 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10566278/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Perioperative glycemic variability (GV) reflects systemic metabolic stress and correlates with postoperative morbidity. However, its specific impact in non-diabetic patients undergoing upfront gastrectomy for early-stage gastric cancer remains unclear. This study evaluated the association between perioperative GV and postoperative infectious complications in non-diabetic patients undergoing curative resection for Stage I–II gastric cancer.

Methods

This retrospective cohort study evaluated 166 consecutive non-diabetic patients with Stage I–II gastric adenocarcinoma undergoing elective upfront gastrectomy (2020–2025). Patients with diabetes, neoadjuvant therapy, or advanced disease were excluded. GV was calculated as the coefficient of variation (CV, %) using central laboratory venous glucose measured twice daily on postoperative days (POD) 0, 1, and 2. Receiver operating characteristic (ROC) curve analysis determined optimal GV cutoffs. Primary outcomes were 30-day infectious complications (surgical site infections [SSIs] and pneumonia) per Centers for Disease Control (CDC) and Prevention CDC criteria. Multivariable logistic regression identified independent risk factors.

Results

Infectious complications occurred in 33.1% (n = 55) of the cohort. ROC analysis established a POD 2 GV cutoff of 7.51% to stratify patients into Low GV (< 7.51%, n = 64) and High GV (≥ 7.51%, n = 102) groups. High GV patients were significantly older with higher American Society of Anesthesiologists (ASA) scores ($p < 0.05$), while BMI, surgical approach, resection extent, and operative time were comparable ($p > 0.05$). Infectious complications were significantly higher in the High GV group (40.2% vs. 21.9%, $p = 0.015$), driven by postoperative pneumonia (28.4% vs. 12.5%, $p = 0.016$) and organ/space SSIs (16.7% vs. 6.2%, $p = 0.049$). Adjusted for age and ASA status, advanced age was an independent risk factor (OR: 1.066, 95% CI: 1.030–1.105, $p < 0.001$), while elevated POD 2 GV showed a strong trend toward increased infection risk (OR: 1.948, 95% CI: 0.905–4.192, $p = 0.088$).

Conclusions

In non-diabetic patients undergoing upfront gastrectomy for early-stage gastric cancer, elevated POD 2 GV was associated with increased postoperative infectious complications, particularly pneumonia and SSIs. Early postoperative GV monitoring may help identify patients at higher infection risk.

INTRODUCTION

Gastric cancer remains a major global public health challenge, ranking among the leading causes of cancer-related mortality worldwide [1]. Surgical resection combined with adequate lymphadenectomy constitutes the cornerstone of treatment for early and resectable gastric cancer [2]. However, despite recent advances in surgical techniques and perioperative care, postoperative complications continue to adversely affect both short-term clinical recovery and long-term oncological outcomes.

Postoperative infectious complications following gastrectomy—including organ/space surgical site infections (SSIs), superficial/deep incisional SSIs, and pneumonia—have been strongly linked to increased morbidity and mortality in patients with gastric cancer [3]. Consequently, identifying risk factors for these complications is paramount to optimizing clinical outcomes and guiding targeted preventive strategies.

Emerging evidence indicates that postoperative uncontrolled hyperglycemia increases the risk of infectious complications in both diabetic and non-diabetic patients, with a clear correlation between the severity of hyperglycemia and complication rates [4]. Notably, Kiran et al. demonstrated that even a single episode of hyperglycemia within the first 72 hours following colorectal surgery was significantly associated with increased morbidity and mortality [5].

Recently, glycemic variability (GV) has emerged as a crucial clinical metric that impacts postoperative outcomes independently of mean or peak glucose levels. GV quantifies the magnitude of perioperative glucose fluctuations, thereby offering a more comprehensive assessment of metabolic dynamics [6]. Mechanistically, pronounced glucose fluctuations have been shown to induce tissue damage by accelerating oxidative stress, endothelial dysfunction, and subclinical inflammation [4, 5, 7].

Existing studies have predominantly focused on diabetic populations or highly heterogeneous cohorts encompassing varying cancer stages, treatment modalities, and baseline metabolic profiles. Consequently, the specific impact of surgical stress-induced GV on postoperative complications in gastric cancer remains poorly defined. To address this gap, the present study aimed to evaluate the association between perioperative GV and infectious complications in a homogenous cohort of non-diabetic patients undergoing curative resection for early-stage gastric cancer.

METHODS

Study Population and Ethical Considerations

This retrospective cohort study evaluated consecutive patients diagnosed with gastric adenocarcinoma who underwent elective curative-intent gastrectomy at a single tertiary center between 2020 and 2025. The study protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (TABED 1.26.2789) and was conducted in strict accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- Age ≥ 18 years
- Histopathologically confirmed gastric adenocarcinoma
- Elective curative-intent gastrectomy without prior neoadjuvant therapy (upfront surgery)
- Pathologically confirmed Stage I–II disease (according to the AJCC/UICC TNM staging system)
- Preoperative normoglycemia or borderline impaired fasting glucose (fasting blood glucose level < 126 mg/dL

Exclusion criteria were as follows:

- Known diagnosis of diabetes mellitus (Type 1 or Type 2) or active use of any antidiabetic medication (insulin or oral hypoglycemic agents)
- Preoperative evidence or intraoperative discovery of distant metastases
- Emergency or palliative surgical interventions
- History of other concurrent or previous malignancies within the past 5 years
- Systemic corticosteroid therapy within the 3 months prior to surgery
- Incomplete perioperative clinical or glycemic follow-up data (FIGURE 1)

Data Collection and Variable Definitions

Demographic, clinical, perioperative, and outcome data were retrospectively extracted from the hospital's electronic health record system and surgical charts.

- **Baseline Demographic and Clinical Characteristics**: Age, sex, body mass index (BMI), ASA, physical status classification, and the Charlson Comorbidity Index (CCI).
- **Surgical and Perioperative Parameters**: Surgical approach (open, laparoscopic, or robotic), extent of resection (total or subtotal gastrectomy), operative time (minutes), and intraoperative red blood cell transfusion requirements.
- **Postoperative Clinical Outcomes**: 30-day postoperative mortality, length of hospital stay, and overall postoperative complications. Complication severity was graded according to the Clavien-Dindo classification (with Grade ≥ III defined as major complications).
- **Infectious Complications**: Primary outcome measures included organ/space SSIs, superficial/deep incisional SSIs, and postoperative pneumonia, diagnosed based on the Centers for Disease Control and Prevention (CDC) criteria.

Definition and Classification of Infectious Complications

Postoperative infectious complications were identified and classified according to the CDC criteria [8]. The infectious outcomes were categorized into specific entities:

- **Organ/Space SSIs**: Defined as intra-abdominal abscesses, fluid collections, or peritonitis involving any part of the anatomy opened or manipulated during the index procedure, confirmed via ultrasonography, computed tomography (CT), or reoperation/percutaneous drainage.
- **Incisional SSIs**: Comprising superficial and deep incisional infections confined to the skin, subcutaneous tissue, or fascial/muscle layers of the surgical incision, exhibiting purulent drainage, localized inflammatory signs, or positive microbiological cultures.
- **Postoperative Pneumonia**: Diagnosed based on the emergence of new or progressive pulmonary infiltrates on chest radiograph or CT scan, accompanied by at least two clinical/laboratory signs of respiratory infection.

Surgical Procedure and Perioperative Management

All surgical procedures were performed by senior upper gastrointestinal surgical oncologists in accordance with the Japanese Gastric Cancer Association (JGCA) treatment guidelines [2], utilizing standard D2 lymphadenectomy. Perioperative management followed a standardized clinical pathway across the cohort. During the early postoperative period (postoperative days [POD] 0 to 2), patients were maintained on strict nil per os status without oral intake or parenteral nutrition. Intravenous maintenance fluid therapy was standardized for all patients using 0.9% sodium chloride and 5% dextrose solutions.

Glucose Monitoring and Glycemic Variability Analysis

To mitigate analytical variance and capillary glucometer inaccuracies related to early postoperative peripheral edema or tissue hypoperfusion, all blood glucose measurements were performed exclusively using venous blood samples in the central laboratory. Following the routine clinical follow-up protocol without active glycemic intervention, capillary or bedside finger-stick values were excluded. Venous blood glucose concentrations were measured twice daily: upon admission to the surgical recovery unit on POD 0, and routinely at 06:00 and 23:00 on POD 1 and POD 2. GV was quantified for each patient using the coefficient of variation (CV, %), calculated using the following standard formula: [CV = (Standard Deviation / Mean Glucose) × 100]. In this study, CV (%) served as the primary metric of GV, while standard deviation (SD, mg/dL) and mean blood glucose concentration were analyzed as secondary parameters.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were evaluated for normal distribution using the Shapiro-Wilk test along with visual inspection of histograms and Q-Q plots. Normally distributed continuous variables are presented as mean±standard deviation (SD), whereas non-normally distributed continuous variables are reported as median with interquartile range (IQR, 25th–75th percentiles). Categorical variables are expressed as absolute frequencies and percentages (n, %).To evaluate the predictive capacity of glycemic variability (GV) for postoperative infectious complications and to establish the optimal predictive time window, receiver operating characteristic (ROC) curve analyses were conducted for individual postoperative days (POD 0, POD 1, POD 2) and overall cumulative GV (POD 0–2). The area under the ROC curve (AUC) with corresponding 95% confidence intervals (CI) was calculated for each timeframe. The optimal cut-off value for GV was determined using Youden's index based on the ROC curve exhibiting the highest diagnostic accuracy.Patients were subsequently dichotomized into "Low GV" and "High GV" groups according to the derived threshold. Group comparisons for continuous variables were performed using the independent-samples Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test for sparse matrices.To identify independent risk factors for postoperative infectious complications, variables demonstrating statistical significance ($p < 0.05$) or clinical relevance in univariate analysis were included in a multivariable binary logistic regression model using a backward stepwise selection method. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test. Results are expressed as odds ratios (ORs) with 95% CIs. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

Patient Baseline Characteristics and Study Cohort

A total of 166 non-diabetic patients who underwent curative-intent surgery for early-stage gastric cancer were included in the final analysis. The overall median age was 64 years (range: 20–92 years; IQR: 16.25), and 71.1% (n = 118) were male. Postoperative infectious complications developed in 33.1% (n = 55) of the cohort. The predictive capacity of GV across individual postoperative days for identifying infectious complications is detailed in Fig. 2 and Table 1. Based on the ROC curve analysis, a threshold value of 7.51% for POD 2 GV demonstrated the highest diagnostic accuracy.

Table 1
The Predictive Power of Glycemic Variability Values at Different Measurement Times for Infectious Complications (ROC Analysis Results)

Time of Measurement	AUC	95% Confidence Interval (CI)	P-value	Optimal Cut-off (%)	Sensitivity (%)	Specificity (%)
POD 0 GV	0.488	0.395–0.581	0.797	> 5.46	76.3	31.5
POD 1 GV	0.535	0.437–0.633	0.464	> 25.93	27.2	89.1
Overall GV	0.567	0.477–0.657	0.158	> 22.06	76.3	42.3
POD 2 GV	**0.603**	**0.512–0.693**	**0.032***	**> 7.51**	**74.5**	**45.0**

* $p < 0.05$ is considered statistically significant.

Patients were subsequently stratified into two cohorts according to this cutoff: the Low GV group (< 7.51%, n = 64, 38.6%) and the High GV group (≥ 7.51%, n = 102, 61.4%).Comparative analysis of baseline characteristics revealed that patients in the High GV group had a significantly higher median age (p = 0.027), higher prevalence of hypertension (p = 0.036), and a larger proportion of individuals with an ASA ≥ 3 (p = 0.029). In contrast, sex distribution, BMI, and preoperative laboratory parameters—including fasting blood glucose and serum albumin levels—were comparable between the two groups (p > 0.05 for all) (Table 2).

Table 2
Baseline Demographics, Comorbidities, and Preoperative Laboratory Data

Variables	Total Cohort(n = 166)	Low GV (< 7.51%) (n = 64)	High GV (≥ 7.51%) (n = 102)	P-value
Age (years) †	64 (20–92), IQR: 15.8	62 (20–90), IQR: 12.2	66 (26–92), IQR: 18.5	**0.027***
Gender (Male), n (%)	118 (71.1%)	49 (76.6%)	69 (67.6%)	0.218
BMI (kg/m²) †	24.3 (14.0–40.8), IQR: 6.2	24.1 (14.0–38.3), IQR: 4.7	24.6 (15.7–40.8), IQR: 6.6	0.299
Smoking, n (%)	75 (45.2%)	25 (39.1%)	50 (49.0%)	0.210
Hypertension, n (%)	66 (39.8%)	19 (29.7%)	47 (46.1%)	**0.036***
CAD, n (%)	45 (27.1%)	14 (21.9%)	31 (30.4%)	0.230
COPD, n (%)	9 (5.4%)	6 (9.4%)	3 (2.9%)	0.089
ASA Score ≥ 3, n (%)	64 (38.6%)	18 (28.1%)	46 (45.1%)	**0.029***
Charlson Index †	4 (2–7), IQR: 2.0	4 (2–7), IQR: 2.0	4 (2–7), IQR: 2.0	**0.043***
Preop Glucose (mg/dL) †	90 (53–120), IQR: 13.0	89 (63–112), IQR: 13.0	90.5 (53–120), IQR: 16	0.456
Preop Albumin (g/L) ‡	41.4 ± 4.0	40.9 ± 3.7	41.6 ± 4.2	0.240
Preop Hemoglobin (g/dL) ‡	12.1 ± 2.0	11.8 ± 1.9	12.2 ± 2.1	0.187

† Non-normally distributed continuous variables are presented as Median (Min-Max), Interquartile Range (IQR) and analyzed using the Mann-Whitney U test.

‡ Normally distributed continuous variables are presented as Mean ± Standard Deviation (SD) and analyzed using the Independent Samples t-test.

Categorical variables are presented as frequencies (%) and analyzed using the Pearson Chi-Square or Fisher's Exact test.

* Indicates statistical significance ($p < 0.05$)

Operative Outcomes and Infectious Complications

Operative characteristics—including surgical approach (open, laparoscopic, or robotic), extent of gastric resection (total vs. subtotal gastrectomy), total operative time, and length of hospital stay—showed no statistically significant differences between the Low GV and High GV groups ($p > 0.05$ for all).However, the overall incidence of postoperative infectious complications was significantly higher in the High GV

group compared to the Low GV group (40.2% vs. 21.9%, p = 0.015). Subgroup analysis of specific infectious entities demonstrated that patients in the High GV group experienced a significantly higher rate of postoperative pneumonia (28.4% vs. 12.5%, p = 0.016) as well as organ/space SSIs (16.7% vs. 6.2%, p = 0.049) (Table 3).

Table 3
Perioperative Details and Postoperative Clinical Outcomes

Variables	Total Cohort(n = 166)	Low GV (< 7.51%) (n = 64)	High GV (≥ 7.51%) (n = 102)	P-value
Surgical Technique, n (%)				0.531
- Open	128 (77.1%)	52 (81.3%)	76 (74.5%)	
- Laparoscopic	23 (13.9%)	8 (12.5%)	15 (14.7%)	
- Robotic	15 (9.0%)	4 (6.3%)	11 (10.8%)	
Resection Type, n (%)				0.459
- Subtotal Gastrectomy	89 (%53.6)	32 (%50)	57 (%55.9)	
- Total Gastrectomy	77 (%46.4)	32 (%50)	45 (%44.1)	
Operation Time (min) †	160 (100–270), IQR: 30.0	160 (120–240), IQR: 30.0	168 (100–270), IQR: 33.8	0.080
Blood Transfusion, n (%)	40 (24.1%)	15 (23.4%)	25 (24.5%)	1.000
Infectious Complications, n (%)	55 (33.1%)	14 (21.9%)	41 (40.2%)	**0.015***
- Pneumonia, n (%)	37 (22.3%)	8 (12.5%)	29 (28.4%)	**0.016***
- Organ/Space SSI, n (%)	21 (12.7%)	4 (6.2%)	17 (16.7%)	**0.049***
- Superficial Incisional SSI, n (%)	21 (12.7%)	5 (7.8%)	16 (15.7%)	0.137
Anastomotic Leak, n (%)	4 (2.4%)	1 (1.6%)	3 (2.9%)	1.000
Clavien-Dindo Grade ≥ 3, n (%)	15 (9.0%)	4 (6.2%)	11 (10.8%)	0.321
Length of Hospital Stay (days) †	8 (4–100), IQR: 3.0	8 (4–100), IQR: 3.0	8 (4–48), IQR: 3.0	0.928
Mortality, n (%)	2 (1.2%)	1 (1.6%)	1 (1.0%)	1.000

† Non-normally distributed continuous variables are presented as Median (Min-Max), Interquartile Range (IQR) and analyzed using the Mann-Whitney U test.

Categorical variables are presented as frequencies (%) and analyzed using the Pearson Chi-Square or Fisher's Exact test.

* Indicates statistical significance ($p < 0.05$).

Multivariable Logistic Regression Analysis

Multivariable logistic regression analysis was performed to evaluate independent predictors of total infectious complications. Advanced age was identified as an independent risk factor (Odds Ratio [OR]: 1.066, 95% Confidence Interval [CI]: 1.030–1.105, $p < 0.001$).In the multivariable model adjusted for age and ASA physical status score, elevated POD 2 GV displayed a strong trend toward an increased risk of infectious complications, though it did not achieve statistical significance (adjusted OR: 1.948, 95% CI: 0.905–4.192, $p = 0.088$) (Table 4).

Table 4
Multivariable Logistic Regression Analysis for Predictors of Total Infectious Complications

Variables	B	Standard Error	P-value	Odds Ratio (95% CI)
Age	0.064	0.018	**< 0.001**	1.066 (1.030–1.105)
ASA Score (III-IV vs I-II)	0.341	0.395	0.388	1.406 (0.648–3.050)
POD2 GV (High vs Low)	0.667	0.391	0.088	1.948 (0.905–4.192)

DISCUSSION

The principal finding of this study is that POD 2 GV is significantly associated with overall infectious complications in non-diabetic patients undergoing upfront curative-intent gastrectomy for early-stage gastric cancer. By explicitly excluding patients with pre-existing impaired glucose metabolism, advanced-stage cancer-induced metabolic derangements, and those receiving neoadjuvant systemic therapy, our study population minimized major confounding factors. Consequently, these findings suggest that the observed perioperative glycemic fluctuations primarily reflect the intrinsic systemic metabolic and neuroendocrine stress response to surgical trauma.

Postoperative hyperglycemia is encountered in up to 50% of surgical patients within the first 48 hours of admission to the intensive care unit [9]. The clinical impact of perioperative hyperglycemia and glycemic fluctuations on surgical outcomes continues to receive increasing attention across various surgical subspecialties. Indeed, Subramaniam et al. demonstrated that GV within the initial 24 hours postoperatively was significantly associated with deep sternal wound infections in patients undergoing coronary artery bypass grafting [10]. Similarly, McConnell et al. reported that blood glucose levels exceeding > 200 mg/dL on POD 2 in diabetic patients following colorectal surgery increased the risk of surgical site infections nearly fourfold (OR = 3.6, $p = 0.02$) [11]. In the setting of gastrointestinal oncology, Yang et al. suggested that elevated glycemic variability on the first postoperative day serves as an independent risk factor for infection-related complications, identifying a POD 1 GV cut-off value of 21.1%

[12]. However, their study cohort was heterogeneous, encompassing mixed cases of gastric, colon, and rectal cancers. In another study, Goh et al. observed that high cumulative GV calculated over the entire duration of hospitalization was linked to an increased overall risk of infection and morbidity [13]. Nevertheless, we contend that such overall cumulative GV metrics spanning the whole hospital stay obscure day-specific acute fluctuations and mask temporal biological peaks driven by surgical stress. In contrast, in our homogenous cohort undergoing upfront curative gastrectomy, the predictive value of GV for infectious complications achieved statistical significance specifically on POD 2. This observation aligns robustly with surgical pathophysiology, as the surge of pro-inflammatory cytokines and surgical stress-induced insulin resistance typically peak around 48 hours postoperatively [14]. Furthermore, early subclinical infectious processes may manifest initial metabolic signals around POD 2. Conversely, blood glucose measurements obtained during the immediate postoperative window (POD 0 and POD 1) are frequently confounded by intraoperative anesthetic agents, surgical trauma-induced catecholamine surges, and fluid/hemodynamic manipulations.

GV quantifies glucose fluctuations independently of absolute mean blood glucose concentrations; indeed, markedly divergent GV profiles can exist among patients exhibiting identical average glucose levels [15]. Consequently, the assessment of GV has gained increasing prominence in predicting clinical outcomes. Following gastrectomy, pronounced glycemic oscillations routinely occur as a consequence of altered gastrointestinal anatomy, accelerated transit time, and modified neuroendocrine signaling [6].In vitro and translational models have demonstrated that intermittent glucose fluctuations exert more harmful cellular effects than sustained hyperglycemia, triggering accelerated cellular apoptosis, oxidative stress, and a surge in pro-inflammatory cytokines [15]. Furthermore, these acute glycemic spikes induce microvascular endothelial dysfunction, impair tissue perfusion, and propagate widespread systemic inflammation [6].Consistent with these pathophysiological insights, previous studies in gastrointestinal oncological surgery have reported that elevated GV significantly increases the risk of postoperative infectious complications [11, 12]. Similarly, a expanding body of literature corroborates the association between high GV and overall surgical morbidity [10, 13, 16]. In our multivariable regression model, although the predictive effect of POD 2 GV did not reach strict statistical significance after adjusting for age and ASA physical status score—remaining as a strong clinical trend (OR = 1.95, 95%CI: 0.905–4.192, p = 0.088)—the significantly higher rates of postoperative pneumonia and organ/space SSIs observed in the High GV group in univariate analysis highlight glycemic variability as a valuable supplementary marker. These findings suggest that early postoperative glycemic fluctuations warrant close clinical surveillance during post-gastrectomy care.

Another noteworthy finding of our study is that advanced age was identified as an independent risk factor for postoperative infectious complications (OR = 1.066, 95%CI: 1.030–1.105, p < 0.001). This observation aligns with a large-scale study by Kunisaki et al., which demonstrated that advanced age independently increases the incidence of postoperative infectious morbidities, including pneumonia and sepsis, in patients undergoing gastrectomy for gastric cancer [3]. Similarly, Rangasamy et al. reported a significantly higher rate of postoperative complications among elderly patients undergoing major surgery [16].Conversely, conflicting reports exist in the literature; for instance, some studies have observed no

significant association between age and infectious complications in gastrectomy cohorts [17]. We contend that this discrepancy largely stems from methodological differences. Specifically, those cohorts exclusively enrolled patients aged 65 years and older—thereby limiting age variance across groups—and exhibited substantial heterogeneity regarding tumor stage and the administration of neoadjuvant systemic therapy. In contrast, our study evaluated a highly homogenous, non-diabetic cohort undergoing upfront surgery for early-stage disease, thereby isolating age as a distinct clinical variable.

A major strength of our study lies in its strict methodological design, which established a highly homogeneous patient cohort to minimize major biological and clinical confounders influencing perioperative glucose metabolism. In contrast, several studies in the literature evaluating the impact of GV on postoperative outcomes merged diabetic and non-diabetic populations within a single analytical cohort [12, 18, 19]. By explicitly excluding patients with known diabetes mellitus, we eliminated the baseline confounding effects of chronic metabolic dysregulation. This approach allowed us to demonstrate that surgical stress-induced glycemic variability serves as an indicator of postoperative infectious processes even in non-diabetic individuals.

Furthermore, a significant limitation in existing literature on glycemic parameters in gastrointestinal oncological surgery is the lack of standardization regarding tumor stage and neoadjuvant systemic therapy [5, 6, 12, 20]. Cytotoxic chemotherapeutic agents have been shown to directly cause pancreatic beta-cell toxicity, impairing insulin biosynthesis and secretion—a functional deficit that often persists well beyond the completion of therapy [21]. Additionally, adjunctive glucocorticoids administered to prevent chemotherapy-induced nausea and hypersensitivity routinely promote severe insulin resistance and glycemic spikes [22]. Moreover, advanced-stage disease and systemic cytotoxic therapy trigger pro-inflammatory cytokine release and drive cancer-related cachexia, which inherently exacerbates glucose fluctuations and metabolic resistance independently of surgical trauma [23]. By excluding patients receiving neoadjuvant therapy or presenting with advanced-stage disease, our study effectively isolated surgical stress as the primary driver of glycemic variability.

By selectively evaluating this homogeneous cohort—devoid of neoadjuvant systemic therapy and advanced-stage disease—our study increases the likelihood that the observed GV predominantly reflects the intrinsic neuroendocrine stress response to surgical trauma, rather than confounding metabolic derangements driven by tumor burden or cytotoxic treatments.

Nevertheless, several methodological limitations of our study should be acknowledged. First, its retrospective, single-center design inherits inherent selection biases and limits the generalizability of our findings. Second, postoperative glycemic monitoring was restricted to twice-daily venous blood sampling in accordance with standard institutional protocols, rather than continuous glucose monitoring (CGM) or high-frequency point-of-care testing. Although CGM systems capture short-term intraday dynamic fluctuations with superior temporal resolution, our reliance on central laboratory venous measurements eliminated capillary glucometer inaccuracies related to tissue edema and hypoperfusion, thereby enhancing data reliability and accuracy. Finally, the narrow physiological range of glucose

fluctuations within this non-diabetic, early-stage cohort may have contributed to the modest discriminatory power (AUC: 0.603) of POD 2 GV. Consequently, POD 2 GV should not be viewed as a standalone diagnostic biomarker, but rather as a non-invasive, supplementary physiological parameter integrated into comprehensive clinical and surgical risk assessment models.

CONCLUSION

In conclusion, within a highly homogeneous cohort of non-diabetic patients undergoing upfront curative gastrectomy for early-stage gastric cancer without neoadjuvant therapy, POD 2 GV was associated with an increased incidence of overall postoperative infectious complications, specifically pneumonia and surgical site infections. Although elevated POD 2 GV did not reach strict statistical significance in multivariable analysis (OR = 1.95, p = 0.088), univariate comparisons and ROC assessment revealed a clinically noteworthy trend toward heightened infection risk in patients exhibiting high GV. Given the strict exclusion criteria of our cohort, these early glycemic fluctuations likely represent an intrinsic systemic metabolic response secondary to surgical trauma. Incorporating POD 2 GV monitoring into early postoperative care pathways may assist clinicians in identifying patients at higher risk for infectious complications and optimizing tailored glycemic management strategies. Larger, multi-center prospective studies with higher glucose sampling frequencies (such as continuous glucose monitoring) are warranted to validate these findings and evaluate their clinical utility.

Abbreviations

AJCC
American Joint Committee on Cancer
ASA
American Society of Anesthesiologists
AUC
Area Under the Curve
BMI
Body Mass Index
CAD
Coronary Artery Disease
CCI
Charlson Comorbidity Index
CDC
Centers for Disease Control and Prevention
CGM
Continuous Glucose Monitoring
CI
Confidence Interval
COPD

Chronic Obstructive Pulmonary Disease
CT
Computed Tomography
CV
Coefficient of Variation
GV
Glycemic Variability
IQR
Interquartile Range
JGCA
Japanese Gastric Cancer Association
OR
Odds Ratio
POD
Postoperative Day
ROC
Receiver Operating Characteristic
SD
Standard Deviation
SPSS
Statistical Package for the Social Sciences
SSI
Surgical Site Infection
TNM
Tumor, Node, Metastasis
UICC
Union for International Cancer Control

Declarations

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (Approval No: TABED 1.26.2789). The requirement for informed consent was waived due to the retrospective design of the study.

Conflict of Interest:

The authors declare no conflict of interest.

Clinical Trial Number:

Not applicable

Consent for publication:

Not applicable

Use of Artificial Intelligence:

The authors used Artificial Intelligence to improve the language and readability of this manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication

Funding statement:

This research received no external funding.

Author Contribution

Conceptualization: CC, SY

Data curation: CC, YOE

Formal analysis: CC, AS, SY

Writing – original draft: CC, SY

Writing – review & editing: CC, AS, SY, YOE

Supervision: AS, SYAll authors reviewed the manuscript.

Acknowledgements

Not applicable

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. https://doi.org/10.3322/caac.21834.
2. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer. 2023;26(1):1–25. https://doi.org/10.1007/s10120-022-01331-8
3. Kunisaki C, Miyata H, Konno H, Saze Z, Hirahara N, Kikuchi H, et al. Modeling preoperative risk factors for potentially lethal morbidities using a nationwide Japanese web-based database of patients undergoing distal gastrectomy for gastric cancer. Gastric Cancer. 2017;20(3):496–507. https://doi.org/10.1007/s10120-016-0634-0.
4. Fiorillo C, Rosa F, Quero G, Menghi R, Doglietto GB, Alfieri S. Postoperative hyperglycemia in nondiabetic patients after gastric surgery for cancer: perioperative outcomes. Gastric Cancer. 2017;20(3):536–42. https://doi.org/10.1007/s10120-016-0621-5.
5. Kiran RP, Turina M, Hammel J, Fazio V. The clinical significance of an elevated postoperative glucose value in non-diabetic patients after colorectal surgery: evidence for the need for tight glucose control? Ann Surg. 2013;258(4):599–604. https://doi.org/10.1097/SLA.0b013e3182a1f2aa.
6. Ge Y, Wang G, Huang Y, Luo B, Zhang Y. Prognostic significance of postoperative glycemic variability after gastric surgery: a retrospective cohort study and development of a mortality prediction model. Eur J Med Res. 2025;30(1):1303. https://doi.org/10.1186/s40001-025-03501-7.
7. Gorst C, Kwok CS, Aslam S, Oliver S, Valabhji J, Myint PK, et al. Long-term glycemic variability and risk of adverse outcomes: A systematic review and meta-analysis. Diabetes Care. 2015;38(12):2354–69. https://doi.org/10.2337/dc15-1188.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309–32. https://doi.org/10.1016/j.ajic.2008.03.002.
9. Vedantam D, Poman DS, Motwani L, Asif N, Patel A, Anne KK. Stress-Induced Hyperglycemia: Consequences and Management. Cureus. 2022;14(7):e26714. https://doi.org/10.7759/cureus.26714.
10. Subramaniam B, Lerner A, Novack V, Khabbaz K, Paryente-Wiesmann M, Hess P. Increased glycemic variability in patients with elevated preoperative HbA1C predicts adverse outcomes following coronary artery bypass grafting surgery. Anesth Analg. 2014;118(2):277–87. https://doi.org/10.1213/ANE.0000000000000100.
11. McConnell YJ, Johnson PM, Porter GA. Surgical site infections following colorectal surgery in patients with diabetes: association with postoperative hyperglycemia. J Gastrointest Surg. 2009;13(3):508–15. https://doi.org/10.1007/s11605-008-0734-1.
12. Yang Z, Jiang F, Jian M, Liu Y, Zhang Y, Zhang Z, et al. High glycemic variability serves as an independent risk factor for postoperative infection-related complications in patients undergoing

radical surgery for gastric, colon, and rectal cancer. Med (Baltim). 2025;104(7):e41602. https://doi.org/10.1097/MD.0000000000041602.

13. Goh GS, Shohat N, Abdelaal MS, Small I, Thomas T, Ciesielka KA, et al. Serum Glucose Variability Increases the Risk of Complications Following Aseptic Revision Hip and Knee Arthroplasty. J Bone Joint Surg Am. 2022;104(18):1614–20. https://doi.org/10.2106/JBJS.21.00878.
14. Micić D, Lalić N, Djukić V, Stanković S, Trajković G, Oluić B, et al. Influence of IL-6, TNF-α and Hs-CRP on Insulin Sensitivity in Patients after Laparoscopic Cholecystectomy or Open Hernia Repair. J Med Biochem. 2018;37(3):328–35. https://doi.org/10.1515/jomb-2017-0043.
15. Kim Y, Rajan KB, Sims SA, Wroblewski KE, Reutrakul S. Impact of glycemic variability and hypoglycemia on adverse hospital outcomes in non-critically ill patients. Diabetes Res Clin Pract. 2014;103(3):437–43. https://doi.org/10.1016/j.diabres.2013.11.026.
16. Rangasamy V, Xu X, Susheela AT, Subramaniam B. Comparison of Glycemic Variability Indices: Blood Glucose, Risk Index, and Coefficient of Variation in Predicting Adverse Outcomes for Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020;34(7):1794–802. https://doi.org/10.1053/j.jvca.2019.12.032.
17. Iida M, Takeda S, Yamamoto T, Nakashima C, Nishiyama M, Watanabe Y, et al. Risk factors for infectious complications after gastrectomy in older patients. Exp Ther Med. 2024;28(2):319. https://doi.org/10.3892/etm.2024.12608.
18. Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg. 2008;248(4):585–91. https://doi.org/10.1097/SLA.0b013e31818990d1.
19. Shohat N, Foltz C, Restrepo C, Goswami K, Tan T, Parvizi J. Increased postoperative glucose variability is associated with adverse outcomes following orthopaedic surgery. Bone Joint J. 2018;100–B(8):1125–32. https://doi.org/10.1302/0301-620X.100B8.BJJ-2017-1283.R1.
20. Mandolfo N, Berger A, Hammer M. Glycemic variability in patients with gastrointestinal cancer: An integrative review. Eur J Oncol Nurs. 2020;48:101797. https://doi.org/10.1016/j.ejon.2020.101797.
21. Hwangbo Y, Lee EK. Acute hyperglycemia associated with anti-cancer medication. Endocrinol Metab (Seoul). 2017;32(1):23–. https://doi.org/10.3803/EnM.2017.32.1.23. 9.
22. Ahn HR, Kang SY, Youn HJ, Jung SH. Hyperglycemia during Adjuvant Chemotherapy as a Prognostic Factor in Breast Cancer Patients without Diabetes. J Breast Cancer. 2020;23(4):398–409. https://doi.org/10.4048/jbc.2020.23.e44.
23. Porporato PE. Understanding cachexia as a cancer metabolism syndrome. Oncogenesis. 2016;5(2):e200. https://doi.org/10.1038/oncsis.2016.3.

Figures

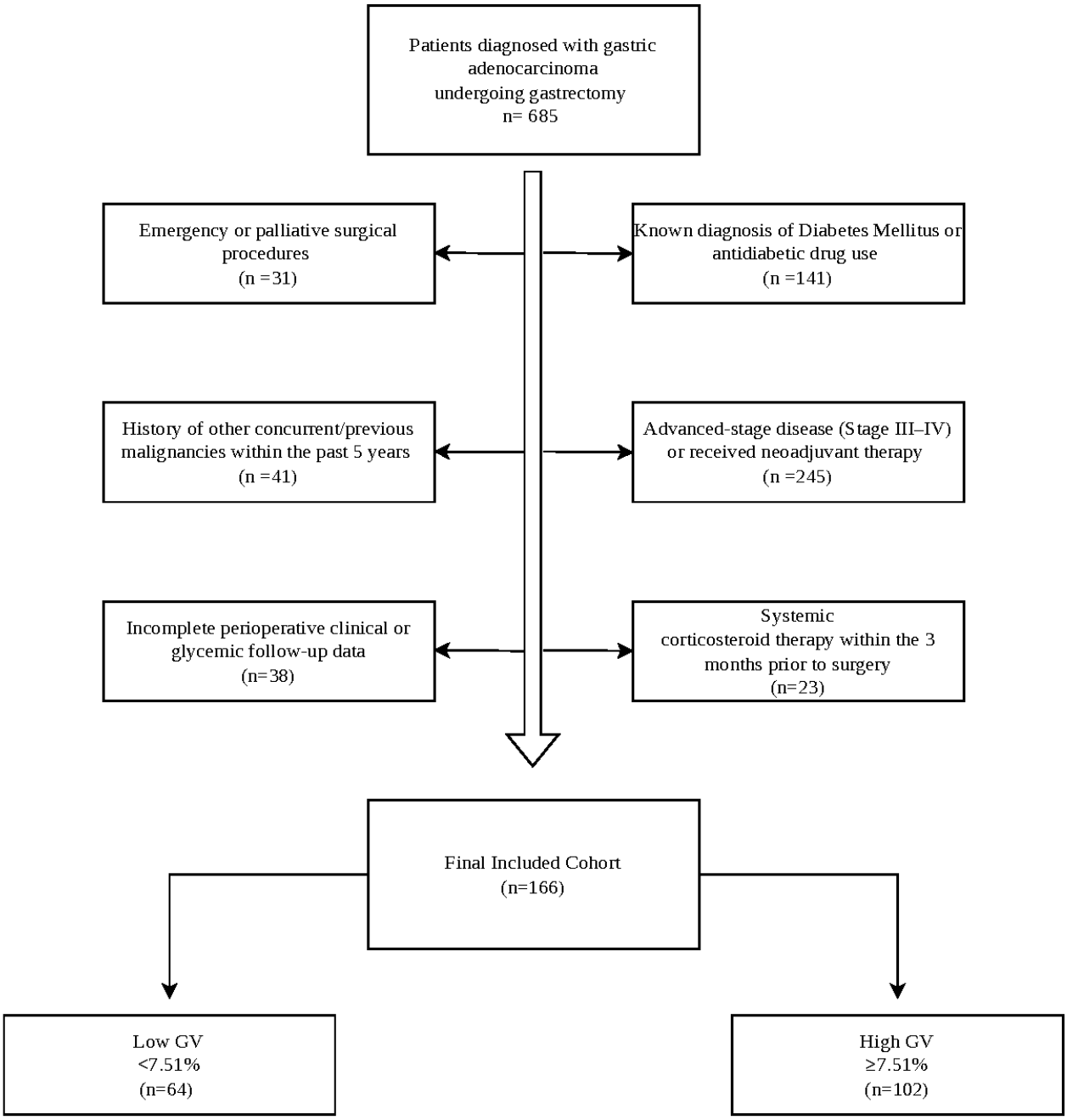


Figure 1

Flowchart

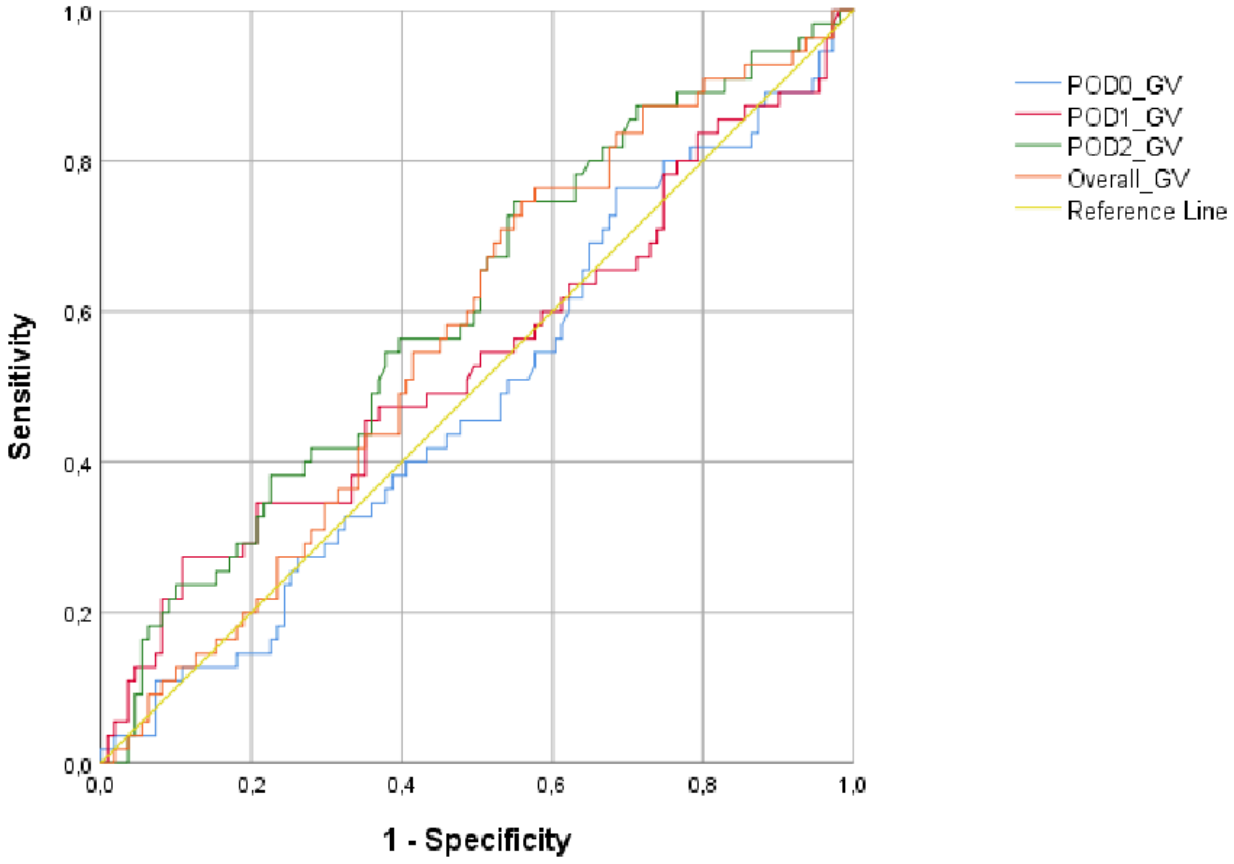


Figure 2

Diagnostic performance of postoperative glycemic variability time points for infectious complications.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklist.doc