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Elevated Glycemic Variability Is an Independent Predictor of ICU and In-Hospital Mortality After Colorectal Cancer Surgery: Retrospective Cohort Analysis and Web-Based Machine-Learning Prediction Model

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Abstract

Background

Colorectal cancer (CRC) is a common malignancy associated with substantial

postoperative mortality and morbidity, particularly among critically ill patients requiring intensive care. Glycemic variability (GV), an emerging marker of glucose dysregulation, has been linked to adverse outcomes in various clinical settings. However, its prognostic value in patients undergoing CRC surgery remains insufficiently characterized. This study aimed to investigate whether GV independently predicts short-term mortality following intensive care unit (ICU) admission in this specific population.

Methods

This retrospective cohort study included 489 adult patients who underwent colorectal cancer surgery and were subsequently admitted to the ICU at The Quzhou Affiliated Hospital of Wenzhou Medical University (Quzhou People's Hospital, Quzhou, China).GV was assessed by calculating the coefficient of variation based on glucose values obtained during the ICU stay. Based on the median threshold of 19%, participants were categorized as a lower GV group (T1) and a higher GV group (T2). The primary endpoint was ICU mortality, while in-hospital mortality served as the secondary outcome. To explore these associations, multivariable logistic regression analyses and Cox proportional hazards models were conducted, complemented by restricted cubic spline (RCS) modeling and Kaplan–Meier survival curves. Furthermore, predictive modeling approaches—including LightGBM, Random Forest, and XGBoost—were implemented to assess prognostic performance, and SHapley Additive exPlanations (SHAP) were employed in enhance model interpretability.

Results

Among the 489 patients, the mean age was 68.75 (12.87) years, and 39.67% were female. Patients in the high GV group exhibited significantly higher ICU mortality (18.44% vs. 5.31%, $P < 0.001$) and in-hospital mortality (25.82% vs. 13.06%, $P < 0.001$). Multivariable analyses demonstrated that elevated GV was independently associated with increased mortality risk across different models (ICU mortality: OR up to 2.95; in-hospital mortality: OR up to 1.57). RCS analysis revealed a significant positive linear relationship between mortality risk and GV. Kaplan–Meier analysis demonstrated a marked reduction in survival probability among patients with higher GV. Subgroup analyses demonstrated that this association remained consistent across most subgroups and was more pronounced in non-diabetic patients. Machine learning models showed moderate predictive performance (AUC up to 0.717), with GV identified as an important predictor alongside severity indicators such as SOFA score and lactate.

Conclusion

Higher glycaemic variability was independently linked to greater likelihoods of both ICU and in-hospital mortality in individuals undergoing colorectal cancer surgery. GV demonstrates a linear relationship with mortality risk and may act as a valuable indicator for risk assessment and individualized management. These findings highlight the clinical importance of maintaining stable glycaemic control in critically ill postoperative CRC patients.

Keywords

Colorectal cancer; Glycaemic variability; ICU; Mortality; Machine learning

1.Introduction

Colorectal cancer (CRC) is a common malignant tumor of the gastrointestinal system, originating mainly from uncontrolled proliferation of colorectal epithelial cells and developing through a multistep process driven by cumulative genetic and molecular changes[1,2]. CRC remains a significant global health concern, consistently ranking among the three most frequently diagnosed malignancies and the leading causes of cancer-related mortality worldwide. Notably, its incidence has shown a rising trend in younger populations in recent years[2]. CRC exhibits substantial biological heterogeneity, with different histological subtypes and degrees of differentiation showing marked differences in invasiveness, metastatic potential, and prognosis[3].

The development of CRC is driven by a complex interplay of genetic mutations, epigenetic alterations, and environmental factors, including dietary patterns, obesity, chronic inflammation, and gut microbiota dysbiosis, which collectively contribute to tumor initiation and progression[4]. Despite significant advances in early screening and multimodal treatment strategies in recent years, CRC remains associated with high incidence and mortality rates, and surgical resection continues to be the cornerstone of treatment[5].

In particular, patients undergoing CRC surgery frequently experience substantial physiological stress, metabolic disturbances, and immune dysregulation, which may

predispose them to postoperative complications, prolonged recovery, and adverse clinical outcomes. However, even after successful tumor removal, patients remain at considerable risk of postoperative complications and mortality[6,7]. Therefore, a deeper understanding of the underlying pathophysiological mechanisms is critical for optimizing risk stratification and informing individualized treatment strategies.

In the intensive care unit (ICU), individuals with CRC frequently exhibit marked metabolic dysregulation. Among these alterations, fluctuations in blood glucose levels—referred to as glycemic variability (GV)—are frequently observed and carry notable clinical significance. Existing evidence suggests that elevated GV is linked to several unfavorable outcomes, such as a higher incidence of infections, extended hospitalization, and increased mortality risk[8]. Nevertheless, its specific impact on postoperative prognosis in patients with CRC remains insufficiently clarified. To further investigate this issue, the present study was conducted in a clearly defined population of adult patients (≥18 years) diagnosed with CRC. Case identification was based on standardized coding systems, specifically the International Classification of Diseases ninth revision codes 153.x and 154.x, as well as tenth revision codes C18.x, C19, and C20, thereby ensuring consistency and diagnostic precision.

To ensure methodological rigor and data independence, a single initial ICU admission per patient with a length of stay ⩾24 hours was included. Furthermore, patients were required to have sufficient glucose monitoring data—specifically, at least three glucose measurements within the first 24 hours—to allow for reliable assessment of GV. Individuals with missing essential demographic information or acute metabolic emergencies such as diabetic ketoacidosis or hyperosmolar hyperglycemic state at admission were excluded to minimize confounding effects. Ultimately, a total of 489 postoperative CRC patients requiring ICU care were incorporated into the analysis.

Within this cohort, participants were divided into low and high GV groups according to the median GV value (19%), enabling comparative evaluation of outcomes across different levels of glycemic fluctuation. The primary endpoint was in-hospital mortality,

defined as death occurring either during the ICU stay or after transfer but before hospital discharge, while ICU mortality was considered a secondary outcome. GV was quantified as the coefficient of variation of blood glucose levels during ICU stay, providing a standardized measure of glucose fluctuation dynamics.

This study sought to investigate the relationship between GV and in-hospital mortality in patients with colorectal cancer, with the goal of providing evidence to inform clinical decision-making and optimize glycemic control in this group.

2. Methods

2.1 Study design and population

The data used in this study were obtained from the electronic health record system of The Quzhou Affiliated Hospital of Wenzhou Medical University (Quzhou People's Hospital, Quzhou, Zhejiang Province, China). This retrospective cohort included adult patients (≥18 years) with a confirmed diagnosis of colorectal cancer (CRC), identified using International Classification of Diseases Ninth Revision (ICD-9: 153.x, 154.x) and Tenth Revision (ICD-10: C18.x, C19, C20) codes. Comprehensive clinical data, including demographic characteristics, laboratory measurements, vital signs, treatment information, and clinical outcomes, were extracted from the institutional database.

To ensure data independence and the reliability of glycaemic variability (GV) assessment, only the first ICU admission for each patient with a length of stay ≥24 hours was included. Patients were excluded if they had missing essential demographic data, fewer than three glucose measurements within the first 24 hours, or a diagnosis of diabetic ketoacidosis or hyperosmolar hyperglycaemic state at admission. The primary outcome was in-hospital mortality, defined as death occurring during hospitalization (including both ICU and post-ICU periods), while ICU mortality was analyzed as a secondary endpoint.

This study was approved by the Ethics Committee of The Quzhou Affiliated Hospital

of Wenzhou Medical University (Approval No.: 2026-028). Given the retrospective design and use of de-identified routinely collected clinical data, the requirement for informed consent was waived.

A total of 489 patients who underwent colorectal cancer surgery and were subsequently admitted to the ICU were included in the final analysis. Patients were stratified into two groups based on GV: the low GV group (T1, n = 245) and the high GV group (T2, n = 244), using the median GV value (19%) of the cohort as the cutoff.

2.2 Exposure definition

GV was characterized by the coefficient of variation (CV) of glucose measurements obtained during the ICU stay. Specifically, CV was computed as (standard deviation / mean glucose level) × 100%, reflecting the extent of glucose fluctuation over time.

2.3 Outcomes

The main endpoint of interest was death occurring during ICU admission. In addition, mortality during the entire hospital stay was analyzed as a secondary outcome.

2.4 Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) when following a normal distribution, and as median and interquartile range (IQR) when the distribution assumption was not met. Categorical variables were expressed as frequency and corresponding percentage. The chi-square test or Fisher's exact test was applied to compare between groups where appropriate.

The Kaplan–Meier survival analysis was applied to evaluate the results of event occurrence time, and the differences between groups were assessed through the log-rank test.

To further examine the association between GV categories and clinical endpoints, regression analyses were conducted. Model 1 employed univariable Cox proportional

hazards regression to estimate hazard ratios (HRs) along with 95% confidence intervals (CIs) for survival outcomes. Model 2 incorporated all covariates into a multivariable logistic regression framework to assess associations with binary outcomes, with effect estimates expressed as odds ratios (ORs) and corresponding 95% CIs.

In the univariate analysis, Model 3 factors with a P-value less than 0.1 were further entered into and retained in the subsequent multivariate regression model for additional evaluation. In Model 4, the Boruta algorithm was used for variable selection, and the selected features were subsequently entered into and included within the regression model for further analysis. To further evaluate predictive performance, a Light Gradient Boosting Machine (LightGBM) model was developed. Model interpretability was further examined using SHapley Additive exPlanations (SHAP). This included the generation of summary visualizations, ranking of feature contributions, as well as individual force plots to illustrate case-level effects. In parallel, the Boruta algorithm was employed as an additional feature selection approach to confirm the robustness of key predictors.

The predictive ability and overall performance of the model were evaluated through receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated to quantify its discrimination performance.

To investigate whether the association between GV and mortality followed a potential nonlinear pattern, restricted cubic spline (RCS) modeling was conducted.

3. Results

3.1 Baseline characteristics

A total of 489 eligible individuals were identified after applying the inclusion criteria, and these patients were subsequently allocated into two groups according to the predefined classification scheme: T1 (n = 245) and T2 (n = 244).

Compared with patients in the T1 group, those assigned to T2 tended to present with

more severe clinical conditions and an overall less favorable physiological status. Notably, both the Simplified Acute Physiology Score II (SAPS II) [35]and the Sequential Organ Failure Assessment (SOFA) score [36] were markedly higher in the T2 group ($P < 0.001$), suggesting a greater degree of illness severity at the time of ICU admission. In addition, patients in the T2 group had a lower body weight compared with those in T1 (76.77 ± 21.20 vs. 84.20 ± 23.96, $P < 0.001$).

With regard to therapeutic interventions, patients in the T2 group more frequently required mechanical ventilation and vasopressor administration than those in T1 (40.98% vs. 31.84%, $P < 0.05$; 26.64% vs. 16.73%, $P < 0.05$), suggesting a higher dependence on advanced supportive care.

Regarding comorbidities, the prevalence of type 2 diabetes mellitus (T2DM) was higher in the T2 group than in T1 (38.93% vs. 22.04%, $P < 0.001$). By contrast, no significant differences were found between the groups in the rates of myocardial infarction, hypertension, or renal disease (all $P > 0.05$).

Regarding laboratory parameters, both creatinine and lactate levels were notably higher in patients from the T2 group ($P < 0.05$). However, white blood cell counts were similar across groups. Likewise, no meaningful differences were identified in vital signs, such as heart rate and mean arterial pressure (all $P > 0.05$).Furthermore, clinical outcomes differed significantly between the groups. Compared with the T1 group, patients in the T2 group had markedly higher ICU mortality and in-hospital mortality (18.44% vs. 5.31%, $P < 0.001$; 25.82% vs. 13.06%, $P < 0.001$).

Overall, patients in the T2 group were characterized by higher disease severity, increased requirements for organ support therapies, and significantly worse clinical outcomes.

Table 1. Baseline characteristics of original cohort.

	Overall (N=489)	T1 (N=245)	T2 (N=244)	p-value	Missing data (%)
Age	68.75 (12.87)	68.34 (13.24)	69.16 (12.51)	0.51	0.00
Gender (Female)	194 (39.67%)	91 (37.14%)	103 (42.21%)	0.29	0.00
Race					
Asian	8 (1.64%)	4 (1.63%)	4 (1.64%)	0.75	0.00
Black	53 (10.84%)	23 (9.39%)	30 (12.30%)		
White	368 (75.26%)	186 (75.92%)	182 (74.59%)		
Other	60 (12.27%)	32 (13.06%)	28 (11.48%)		
Weight	80.51 (22.91)	84.20 (23.96)	76.77 (21.20)	<0.001	0.82
Severity of illness					
SAPS_II	35.63 (16.13)	32.80 (14.02)	38.46 (17.58)	<0.001	0.00
SOFA_score	5.99 (3.49)	5.42 (3.12)	6.57 (3.74)	<0.001	0.00
Interventions					
MV_therapy (YES)	178 (36.40%)	78 (31.84%)	100 (40.98%)	<0.05	0.00
Vasopressor_therapy (YES)	106 (21.68%)	41 (16.73%)	65 (26.64%)	<0.05	0.00
Comorbidities					
T2DM (YES)	149 (30.47%)	54 (22.04%)	95 (38.93%)	<0.001	0.00
MI (YES)	52 (10.63%)	26 (10.61%)	26 (10.66%)	1	0.00

	Overall (N=489)	T1 (N=245)	T2 (N=244)	p-value	Missing data (%)
Hypertension (YES)	265 (54.19%)	142 (57.96%)	123 (50.41%)	0.11	0.00
Renal (YES)	84 (17.18%)	42 (17.14%)	42 (17.21%)	1	0.00
Vital signs					
Heart_rate	97.33 (22.71)	96.35 (22.66)	98.31 (22.76)	0.32	0.41
MAP	82.06 (21.46)	82.95 (20.49)	81.17 (22.40)	0.23	0.20
Lab tests					
Lactate	3.12 (3.30)	2.23 (2.18)	3.85 (3.86)	<0.001	55.21
Creatinine	1.46 (1.37)	1.35 (1.36)	1.58 (1.38)	<0.05	1.23
WBC_count	12.79 (9.24)	12.71 (9.62)	12.87 (8.87)	0.4	2.04
Outcome					
ICU_mortality (Death)	58 (11.86%)	13 (5.31%)	45 (18.44%)	<0.001	0.00
In-hospital_mortality (Death)	95 (19.43%)	32 (13.06%)	63 (25.82%)	<0.001	0.00

Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Variables in bold have p-value < 0.05.

3.2 Association between glycemic variability and all-cause mortality

RCS analyses (Figure 1) were conducted to further examine the association between GV and mortality across the entire study population. GV was strongly linked to ICU mortality (overall $P < 0.01$), with no evidence of nonlinearity (nonlinear $P = 0.61$), indicating a predominantly linear relationship. The risk of ICU mortality remained relatively stable at lower GV levels but increased progressively as GV rose, particularly

beyond the reference value of approximately 0.19, suggesting a dose–response pattern between GV and ICU mortality risk. Similar findings were noted for in-hospital mortality. GV showed a borderline significant association with in-hospital mortality (overall $P = 0.05$), suggesting a potential relationship that approached statistical significance. Meanwhile, no evidence of a nonlinear pattern was observed (nonlinear P = 0.17), indicating that the association between GV and in-hospital mortality tended to follow a relatively linear trend across the studied range. The curve demonstrated that the hazard ratio was close to 1 around the reference point (GV ≈ 0.19) and increased gradually with higher GV levels, indicating that elevated GV may also be associated with an increased risk of in-hospital mortality, although the strength of this association appeared weaker compared with ICU mortality.

Kaplan–Meier survival analysis (Figure 2) further supported these findings. Patients with higher GV (T2 group) exhibited significantly lower survival probabilities compared with those with lower GV (T1 group). For ICU mortality (Figure 2), the high GV group showed a markedly reduced survival probability (log-rank $P = 0.004$), with a more pronounced decline during the early phase after ICU admission. A comparable trend was also noted for in-hospital mortality (Figure 2). Patients in the higher GV group exhibited significantly poorer survival, as indicated by the log-rank test (P = 0.003).

Elevated glycemic variability was linked to a greater likelihood of death after ICU admission. Moreover, this association appeared to follow an approximately linear pattern across the observed GV spectrum.

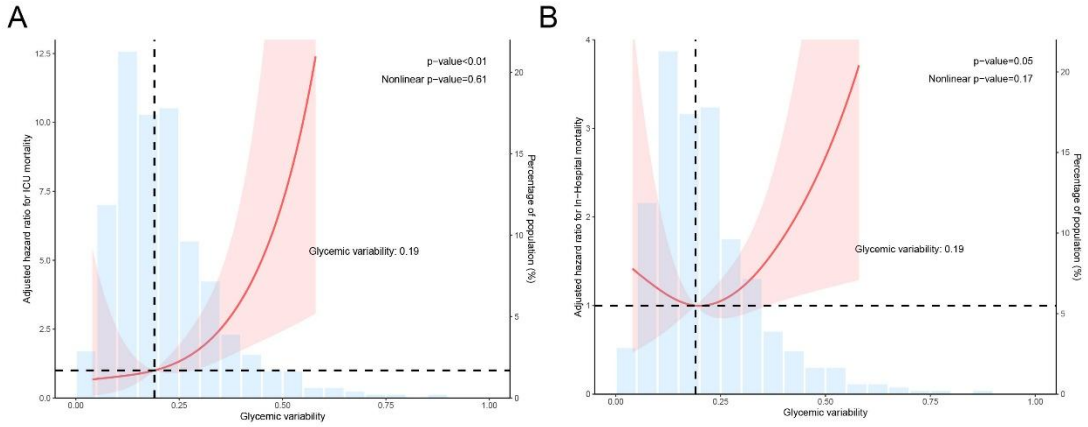


Fig. 1. RCS analyses of the association between GV and mortality in the overall cohort.

(A–B) RCS curves for the association of GV with ICU mortality (A) and in-hospital mortality (B), respectively. Red solid lines represent adjusted HRs, and shaded areas indicate 95% CIs. Blue histograms show the distribution of GV. The horizontal dashed lines indicate HR = 1, and the vertical dashed lines indicate the reference value of GV (0.19). P-values for overall and nonlinear associations are shown in each panel.

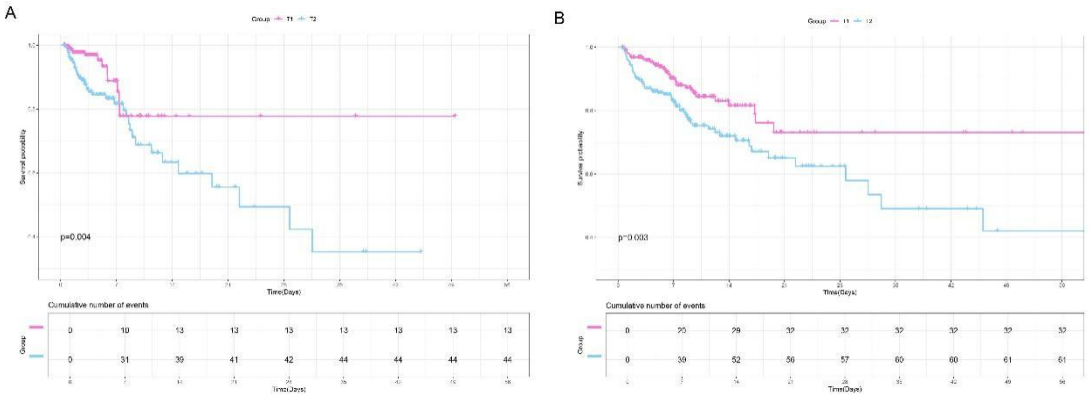


Fig. 2. Kaplan–Meier survival curves stratified by GV groups.

(A – B) Kaplan – Meier survival curves for ICU mortality (A) and in-hospital mortality (B), respectively, in patients stratified into two groups (T1 and T2) according to GV levels. The pink line represents the T1 group (lower GV), and the blue line represents the T2 group (higher GV). Tick marks indicate censored observations. The numbers at risk are shown below each panel.

Kaplan–Meier analysis demonstrated that patients in the T2 group had significantly lower survival

probabilities compared with those in the T1 group for both ICU mortality (log-rank P = 0.004) and in-hospital mortality (log-rank P = 0.003), indicating that higher GV was associated with worse short-term outcomes.

3.3 Cox regression analysis

The findings from the time-dependent univariable Cox proportional hazards models are summarized in Supplementary Tables 1 and 2. In the unadjusted models, elevated GV was linked to a significantly higher risk of mortality.

For ICU mortality (Supplementary Table 1), individuals in the T2 group showed a markedly increased risk compared with those in T1 (HR = 2.46, 95% CI 1.32–4.61, P = 0.005).A similar pattern was observed for in-hospital mortality (Supplementary Table 2), where patients with higher GV remained at greater risk (HR = 1.90, 95% CI 1.24–2.91, P = 0.003).

Overall, the results of the Cox model indicate that an increase in the GV value is associated with an increased risk of death in the intensive care unit and during hospitalization. These findings are consistent with the direction of the multivariate analysis, further confirming the potential predictive value of GV.

3.4 Subgroup analysis

Subgroup analyses were conducted to evaluate the robustness of the association between GV and mortality outcomes across different populations (Figure 3).

Overall, a broadly consistent pattern emerged across most subgroup analyses, indicating that patients with higher GV (T2) tended to have an elevated risk of mortality.

For ICU mortality (Figure 3A), high GV demonstrated a significant relationship with increased risk in the overall cohort (HR = 2.46, 95% CI 1.32–4.61, *P* = 0.005). This relationship remained statistically significant in several strata, including patients aged ⩾65 years (HR = 3.16, 95% CI 1.29–7.70, *P* = 0.011), male patients (HR = 3.08, 95%

CI 1.33–7.16, $P = 0.009$), those with SOFA scores ⩾5 (HR = 2.25, 95% CI 1.17–4.32, $P = 0.015$), and individuals receiving mechanical ventilation (HR = 2.62, 95% CI 1.21–5.71, $P = 0.015$). In contrast, this association was not statistically significant among patients younger than 65 years, females, those with SOFA scores <5, or those who did not receive mechanical ventilation.

Regarding in-hospital mortality (Figure 3), similar trends were observed. Elevated GV was related to a greater likelihood of death in the overall population (HR = 1.90, 95% CI 1.24 – 2.91, $P = 0.003$). This association persisted across multiple subgroups, including both younger (<65 years: HR = 2.12, 95% CI 1.03–4.34, $P = 0.041$) and older patients (⩾65 years: HR = 1.72, 95% CI 1.01–2.93, $P = 0.046$), as well as in females (HR = 2.04, 95% CI 1.03–4.04, $P = 0.041$) and males (HR = 1.79, 95% CI 1.04–3.10, $P = 0.037$). Significant associations were also identified in patients with SOFA scores ⩾5 (HR = 1.91, 95% CI 1.19–3.08, $P = 0.008$) and those undergoing mechanical ventilation (HR = 2.18, 95% CI 1.23 – 3.87, $P = 0.007$). However, no statistically meaningful relationship was detected in subgroups with SOFA scores <5 or in patients who did not receive mechanical ventilation.

Additionally, when stratified by the presence of T2DM, the association between GV and mortality was evident only among patients without diabetes. In this subgroup, higher GV was linked to increased risks of both ICU mortality (HR = 2.55, 95% CI 1.26–5.15, $P = 0.009$) and in-hospital mortality (HR = 2.16, 95% CI 1.32–3.54, $P = 0.002$). In contrast, no statistically significant correlation was found in patients with diabetes.

Notably, interaction testing across all subgroup analyses did not reveal any significant effect modification (all $P > 0.05$), suggesting that the overall association between GV and mortality remained relatively stable across different patient subgroups.

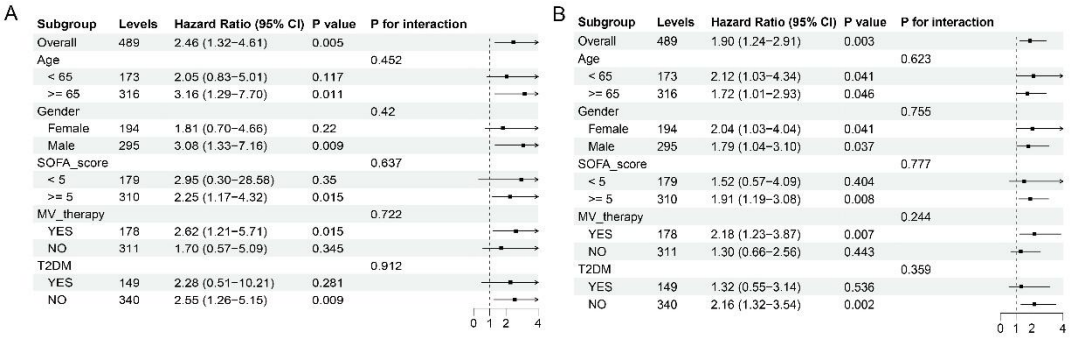


Fig. 3. Subgroup analysis of the association between GV and mortality.

(A–B) Forest plots for the association of GV with ICU mortality (A) and in-hospital mortality (B), respectively. HRs and 95% CIs were estimated using Cox proportional hazards models. Subgroup analyses were stratified by age, gender, SOFA score, MV therapy, and the presence of T2DM.Across most subgroups, higher GV was associated with an increased risk of mortality. The association remained statistically significant in several strata, including older patients (≥65 years), male patients, those with higher SOFA scores (≥5), and those receiving MV therapy. No significant interactions were observed between GV and subgroup variables (P for interaction > 0.05), indicating that the effect of GV on mortality was generally consistent across different patient subgroups.

3.5 Feature importance analysis

Feature attribution analysis was performed to quantify the relative importance of variables across different decision categories (Figure 3). Overall, a clear heterogeneity in feature importance was observed among the confirmed, tentative, rejected, and shadow groups.

In the confirmed group, indicators of disease severity dominated the model's decision-making. The most influential variables included the SAPS II, SOFA score, and lactate level, all of which showed markedly higher importance than other features. This suggests that high-confidence predictions were primarily driven by global severity assessment and metabolic derangement.

In contrast, the tentative group was mainly influenced by physiological parameters and treatment-related variables, including mechanical ventilation, white blood cell count, mean arterial pressure, heart rate, and vasopressor use. These variables demonstrated moderate but consistent contributions, indicating that intermediate clinical status and ongoing supportive therapies play a key role in borderline or uncertain predictions.

For the rejected group, baseline characteristics and chronic comorbidities were more prominent. Key features included renal function, creatinine level, history of myocardial infarction, hypertension, T2DM, age, and sex. Although their overall contributions were smaller than those of acute severity indicators, these variables appeared to contribute to exclusionary decision patterns.

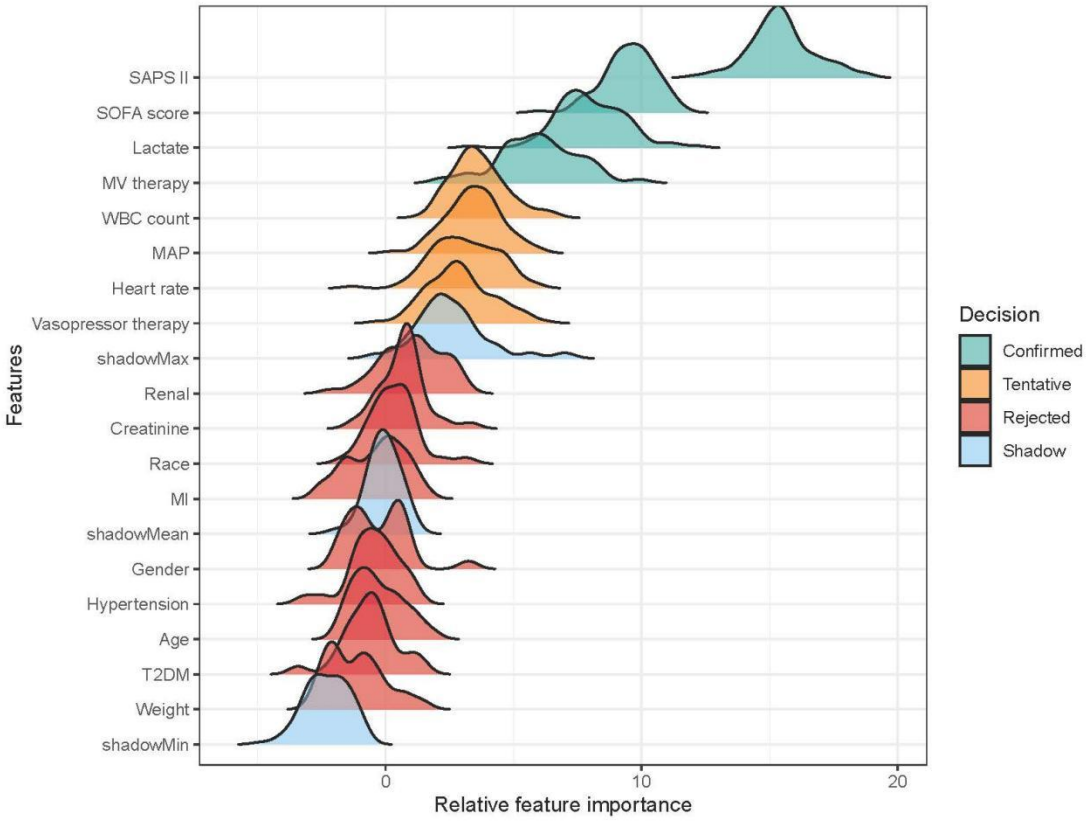


Figure 4. Feature selection using the Boruta algorithm.

Boruta feature selection was performed to identify important predictors associated with mortality. Variables were categorized as “confirmed”, “tentative”, or “rejected” based on their importance compared with shadow features. Key predictors included SAPS II,

SOFA score, lactate level, mechanical ventilation, and hemodynamic parameters, indicating their strong contribution to model performance.

3.6 Machine learning and predictive performance analysis

The performance and interpretability of the machine learning models were evaluated using SHAP and ROC analyses (Figure 5).

SHAP analysis revealed that variables reflecting disease severity had the greatest impact on model predictions. Among the variables included in the model, the SOFA score showed the strongest contribution to prediction. This was followed by the Glasgow Coma Scale (GCS) and lactate levels. In general, increases in these indicators were consistently linked to a higher estimated risk. In contrast, variables such as body weight, vasopressor use, and sex showed relatively limited contributions.

The SHAP-based feature importance ranking further confirmed the dominant role of SOFA score, with GCS and lactate also contributing substantially. Creatinine and body weight showed moderate importance, whereas mean arterial pressure, T2DM, age, and sex had comparatively minor effects on the overall model output.

Individual-level interpretation using SHAP force plots illustrated the additive nature of feature contributions. In representative cases, lower SOFA and GCS values were associated with reduced predicted risk, while other variables exerted smaller and sometimes opposing effects, highlighting the combined influence of multiple clinical features.

Model discrimination was assessed using ROC curves. The Random Forest model achieved the highest performance (AUC = 0.717), followed by XGBoost (AUC = 0.706) and LightGBM (AUC = 0.700). Overall, all models demonstrated moderate and comparable discriminative ability.

Taken together, these findings indicate that severity-related variables play a central role in outcome prediction, while ensemble-based machine learning models provide stable,

albeit moderate, predictive performance in this cohort.

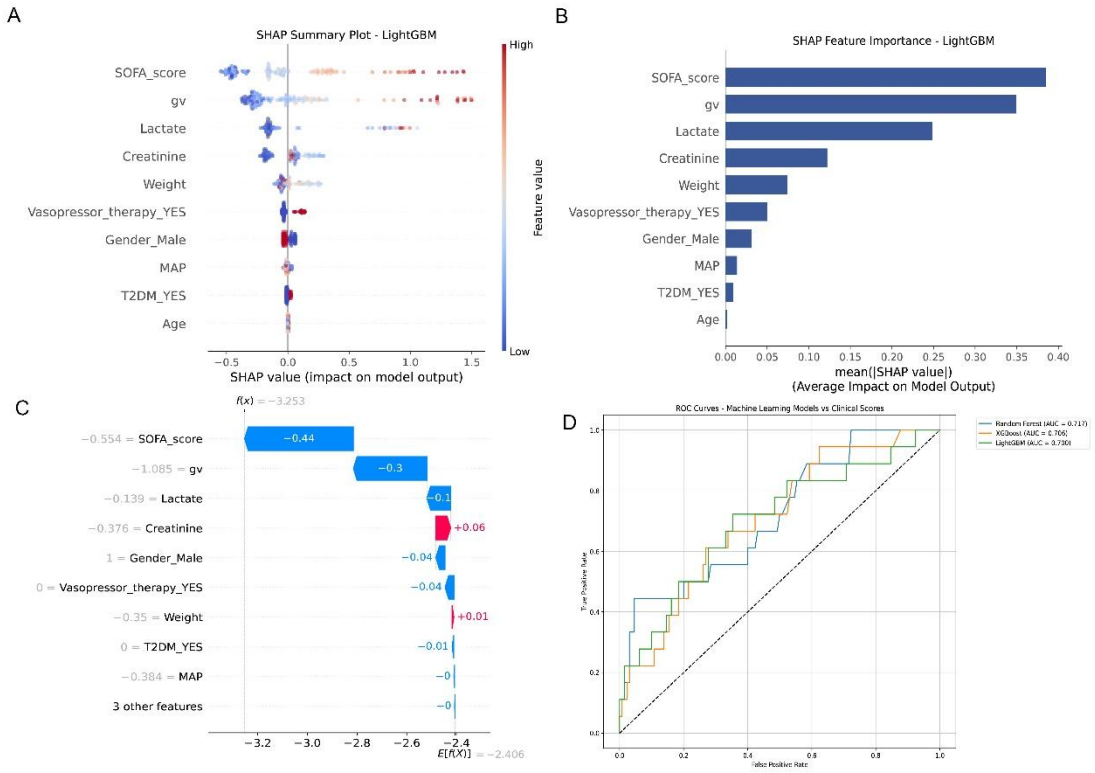


Figure 5. Machine learning model interpretation and performance.

(A)SHAP summary plot showing the impact of each feature on model output. Higher values of SOFA score, GV, and lactate were associated with increased mortality risk.

(B) SHAP feature importance ranking based on mean absolute SHAP values, indicating that SOFA score, GV, and lactate were the most influential predictors.

(C) SHAP force plot illustrating the contribution of individual features to the prediction for a representative patient.

(D) ROC curves comparing the predictive performance of machine learning models. Random Forest achieved the highest performance (AUC = 0.717), followed by XGBoost (AUC = 0.706) and LightGBM (AUC = 0.700).

3.7 Multivariable regression models

To examine the relationship between GV and mortality outcomes, a series of regression

analyses were performed (Table 2 and Supplementary Tables 1–8). In the unadjusted Cox proportional hazards model, patients in the T2 group exhibited a significantly higher risk of death compared with those in T1, both for ICU mortality (HR = 2.46, 95% CI: 1.32–4.61, $P = 0.005$) and in-hospital mortality (HR = 1.90, 95% CI: 1.24–2.91, $P = 0.003$).

After incorporating all relevant covariates into the multivariable logistic regression model (Model 2), the association remained significant. Elevated GV was still linked to increased mortality, with ICU mortality showing an OR of 2.95 (95% CI: 1.38–6.63, $P = 0.007$) and in-hospital mortality an OR of 1.57 (95% CI: 1.39–1.96, $P = 0.02$). Moreover, markers reflecting disease severity, including the SAPS II score and lactate levels, were identified as independent predictors of mortality. In contrast, patients who did not receive mechanical ventilation tended to have a lower risk of death.

The logistic regression model constructed using variables identified in univariable analyses (Model 3) produced similar findings. Patients in the T2 group showed a significantly elevated risk of ICU mortality (OR = 2.56, 95% CI: 1.26–5.45, $P = 0.01$) as well as in-hospital mortality (OR = 1.56, 95% CI: 1.31–1.88, $P = 0.01$).

After further refinement of predictors through the Boruta feature selection method (Model 4), the results remained stable. The T2 group continued to demonstrate increased risks, with an OR of 2.50 (95% CI: 1.24–5.28, $P = 0.01$) for ICU mortality and 1.53 (95% CI: 1.23–1.76, $P = 0.02$) for in-hospital mortality.Overall, the direction of the GV effect was consistent across all models, with HRs/ORs greater than 1. The effect sizes ranged from 1.53 to 2.95 without substantial fluctuation, indicating that the association was not driven by specific model specifications or variable selection strategies. Moreover, all models reached statistical significance ($P < 0.05$), further

supporting the robustness of the findings.

In parallel with traditional regression approaches, machine learning–based models were developed to further evaluate predictive performance and clinical applicability. Consistent with the regression results, GV was identified as an important predictive feature across models. Based on the optimal model, a web-based individualized risk prediction tool was constructed (Fig. 6), allowing clinicians to input patient-specific variables (e.g., age, laboratory indices, comorbidities, and GV) and obtain real-time estimates of mortality risk. This tool translates model outputs into an intuitive clinical interface, thereby facilitating bedside risk stratification and supporting individualized decision-making[9].

Notably, the supplementary materials represent a key strength of this study rather than ancillary content. Supplementary Data 2, derived from an independently collected real-world cohort at our institution, serves as an external validation dataset with inclusion and exclusion criteria largely consistent with the primary databases. This design enables validation of our findings beyond public datasets, thereby enhancing their credibility and generalizability.

Meanwhile, Supplementary Tables 1–8 systematically evaluate the association between GV and mortality in the eICU cohort across multiple modeling strategies, including time-dependent Cox models and multivariable logistic regression with different covariate selection approaches (full adjustment, univariable screening, and Boruta-based selection). The consistency of results across these analyses further supports the robustness of GV as an independent prognostic factor.

Collectively, the combination of multi-model sensitivity analyses, machine learning–based prediction, and external real-world validation substantially strengthens the reliability and clinical applicability of our findings.

Table 2. Primary and secondary outcome analyses with different models for cohort.

		In-hospital mortality		ICU mortality	
Model	Group	p-value	Result	p-value	Result
Model 1[1]	T1		1 (Reference)		1 (Reference)
	T2	<0.01	1.9 (1.24, 2.91)	<0.01	2.46 (1.32, 4.61)
Model 2[1]	T1		1 (Reference)		1 (Reference)
	T2	0.02	1.57 (1.39, 1.96)	<0.01	2.95 (1.38, 6.63)
Model 3[1]	T1		1 (Reference)		1 (Reference)
	T2	0.01	1.56 (1.31, 1.88)	<0.05	2.56 (1.26, 5.45)
Model 4[1]	T1		1 (Reference)		1 (Reference)
	T2	0.02	1.53 (1.23, 1.76)	<0.05	2.5 (1.24, 5.28)

Statistical analyses of different models with p-value < 0.05 were displayed in bold.

[1]OR = Odds Ratio, CI = Confidence Interval.

Model 1: Univariable Cox [HR (95% CI)];

Model 2: Logistic model adjusted with all covariates [OR (95% CI)];

Model 3: Logistic model adjusted with covariates selected by univariable analyses [OR (95% CI)];

Model 4: Logistic model adjusted with covariates selected by Boruta [OR (95% CI)].

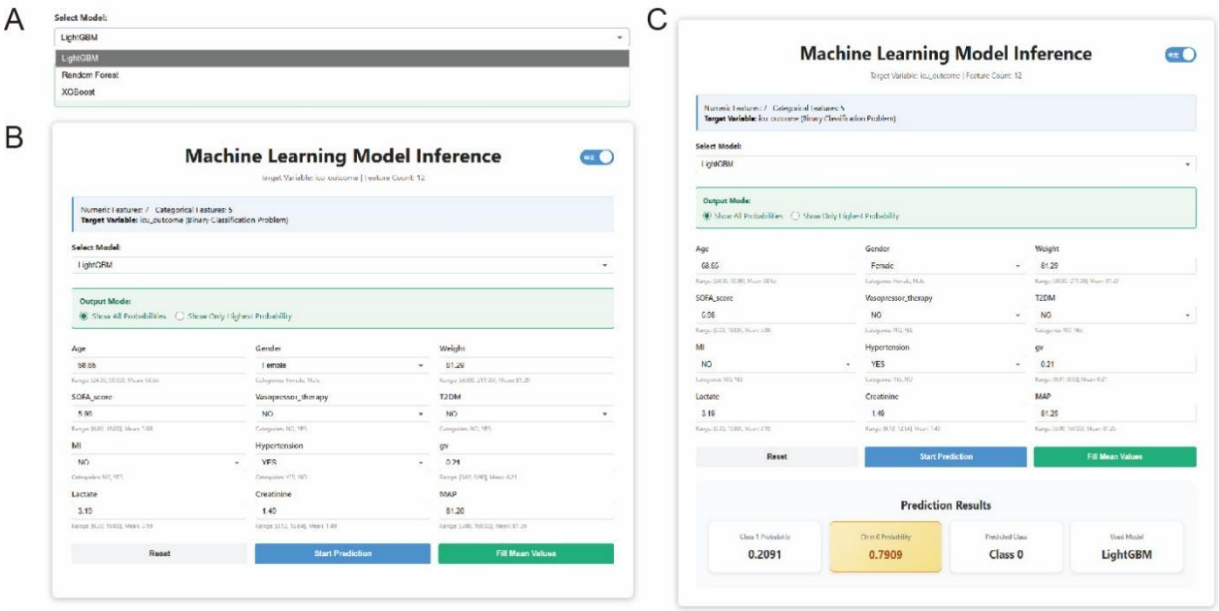


Fig. 6 Web-based individualized risk prediction tool developed from the machine-learning model.

Representative interface of the online prediction platform for critically ill patients incorporating GV. The tool enables input of patient-specific clinical variables and provides personalized estimates of mortality risk, thereby supporting bedside risk stratification and enhancing the clinical applicability of the machine-learning model.

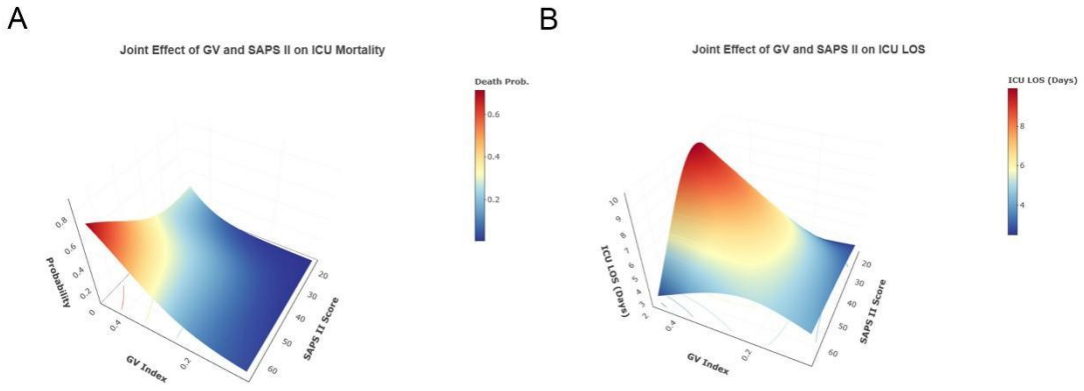


Fig. 7 Joint effects of glycemic variability and SAPS II on ICU mortality and ICU length of stay.

(A) Three-dimensional surface plot illustrating the combined association of GV and

SAPS II score with ICU mortality risk. (B) Three-dimensional surface plot depicting the joint association of GV and SAPS II score with ICU length of stay (ICU LOS).

The surface demonstrates a progressive increase in death probability as both GV and SAPS II increase. At relatively low SAPS II levels, the effect of elevated GV on mortality appears modest; however, when SAPS II exceeds approximately 50, even moderate increases in GV are associated with a steep rise in mortality probability, forming a pronounced high-risk region on the surface plot. This finding suggests a potential synergistic interaction between metabolic instability and overall disease severity, whereby elevated GV may amplify the adverse prognostic impact of critical illness. The steep gradient and concentrated red region indicate a marked escalation in mortality risk among patients with simultaneously high GV and high SAPS II scores (Fig. 7A).

A distinct ridge-like distribution can be observed, with ICU LOS progressively increasing as GV rises, particularly among patients with moderate-to-high SAPS II scores. The peak region indicates that patients with concurrent metabolic instability and severe physiological derangement tend to require substantially prolonged ICU care. Compared with the mortality surface, the ICU LOS plot exhibits a smoother and more continuous curvature, suggesting a gradual accumulation of disease burden and recovery delay across increasing levels of GV and illness severity. Collectively, these findings indicate that elevated GV may not only contribute to higher mortality risk but also increase healthcare resource utilization by prolonging ICU stay (Fig. 7B).

4.Discussion

In this retrospective study utilizing a large-scale ICU database, we explored the relationship between GV and both ICU and in-hospital mortality in patients who underwent colorectal cancer surgery.

Our findings demonstrated that, in this critically ill population, higher GV was

independently associated with an increased risk of both outcomes. These results are consistent with previous studies indicating that GV is an important prognostic factor in critically ill patients. Prior research has shown that glucose fluctuations are associated with adverse outcomes, including increased mortality, higher risk of infection, and prolonged hospital stay, independent of mean glucose levels. Taken together, these observations highlight that dynamic glycemic instability may exert a more pronounced impact on patient prognosis than static glucose measurements alone. In particular, rapid and repeated glucose excursions may aggravate physiological stress responses, thereby contributing to unfavorable clinical trajectories. This underscores the potential value of incorporating GV into routine risk assessment frameworks in the ICU setting.[10-14]. However, most previous studies have focused on general ICU populations or specific disease groups, with limited attention to postoperative colorectal cancer patients. As a result, the potential impact of GV in this particular clinical setting remains insufficiently characterized, and evidence specific to surgical oncology populations is still relatively scarce, highlighting the need for more targeted investigations.

To better characterize population heterogeneity, we applied a stratified phenotyping approach based on GV distribution. Given the substantial variability in GV, analyses based solely on the overall population may obscure subgroup-specific associations due to effect dilution. By dividing patients into T1 and T2 groups using a cutoff value of 0.19, we identified a clear risk gradient, enabling a more precise assessment of the relationship between GV and clinical outcomes. From a clinical perspective, this stratified approach aligns with precision medicine principles and facilitates the transition from average risk estimation to individualized risk assessment.

The association between elevated GV and increased mortality risk may be explained by multiple biological mechanisms. In patients undergoing colorectal cancer surgery, GV may be exacerbated by perioperative factors such as stress-induced hyperglycemia, activation of neuroendocrine stress pathways, insulin resistance, inflammatory responses, and the use of parenteral nutrition or glucocorticoids. These factors often act in combination, leading to pronounced fluctuations in glucose homeostasis during the

postoperative period. In addition, surgical trauma and anesthesia can further disrupt metabolic regulation, thereby amplifying glycemic instability. Such variability may promote oxidative stress, endothelial dysfunction, and immune dysregulation, ultimately contributing to organ dysfunction and poorer clinical outcomes in this high-risk population[15-17]. These factors contribute to postoperative glucose instability and may amplify the adverse effects of GV. Rapid glucose fluctuations are more likely than sustained hyperglycemia to induce oxidative stress by promoting excessive production of reactive oxygen species, leading to endothelial dysfunction, mitochondrial injury, and impaired tissue perfusion. In addition, repeated swings in glucose levels may trigger inflammatory signaling pathways and further disrupt cellular homeostasis, thereby exacerbating tissue damage. Such metabolic instability can also impair microcirculatory function and oxygen delivery, which are critical in the postoperative recovery phase. Collectively, these processes may accelerate organ dysfunction and increase the vulnerability of critically ill patients to adverse outcomes[18]. In addition, GV is associated with enhanced inflammatory responses through activation of pro-inflammatory pathways, resulting in increased cytokine release and amplification of inflammatory cascades, which may be particularly detrimental in postoperative patients[19-21].

Furthermore, glucose instability may impair immune function by disrupting neutrophil activity, reducing phagocytic capacity, and increasing susceptibility to infection, a major contributor to postoperative mortality. In addition, dysregulated glucose levels may alter cytokine production and weaken the coordination of innate and adaptive immune responses, further compromising host defense mechanisms. This impaired immune competence can delay wound healing and increase the risk of secondary complications, such as sepsis or surgical site infections. As a result, patients experiencing pronounced glycemic fluctuations may face a higher likelihood of adverse postoperative trajectories and poorer overall outcomes[22-24]. GV may also reflect underlying disease severity and metabolic dysregulation[25-28]. In our study, patients with higher GV exhibited higher SOFA and SAPS II scores, as well as elevated lactate levels,

indicating more severe illness and impaired tissue perfusion. Therefore, GV may function both as a mediator of adverse outcomes and as a marker of disease severity.

Subgroup analyses showed that the association between GV and mortality was generally consistent across different patient groups, although stronger effects were observed in older patients, those with higher SOFA scores, and those requiring mechanical ventilation. Notably, this association was significant in non-diabetic patients but not in diabetic patients[29-31]. This finding is consistent with previous studies suggesting that chronic hyperglycemia may induce adaptive mechanisms that attenuate the harmful effects of glucose fluctuations, whereas non-diabetic individuals may be more vulnerable to acute metabolic disturbances[32-34].

In addition, machine learning analysis provided complementary evidence supporting the prognostic value of GV. The machine learning–based web prediction tool developed in this study offers several practical and methodological advantages. First, it enables real-time and individualized risk estimation, allowing clinicians to input routinely collected clinical variables and obtain immediate mortality predictions at the bedside. This facilitates dynamic clinical decision-making and enhances risk stratification beyond traditional static models. Feature importance and SHAP analyses consistently identified GV as a relevant predictor, although its contribution was secondary to established severity indicators such as SOFA score and lactate. This suggests that GV should be interpreted within a broader clinical context rather than in isolation. The moderate predictive performance of the models further indicates that accurate outcome prediction requires integration of multiple clinical variables. Notably, the relative importance of GV, although not dominant, remained stable across different modeling approaches, reinforcing its potential role as a supportive prognostic marker. This finding aligns with the concept that complex clinical outcomes in critically ill patients are rarely driven by a single factor but instead reflect the combined effects of physiological derangements and underlying disease severity. Furthermore, SHAP-based interpretation highlighted the heterogeneity of individual risk profiles, suggesting that the impact of GV may vary across patients depending on baseline characteristics

and clinical conditions. These results emphasize the necessity of incorporating GV into multidimensional risk assessment frameworks alongside traditional severity scores and biochemical markers. In practice, such an integrative approach may improve the precision of prognostic evaluation and facilitate more individualized clinical decision-making.

In addition, multiple machine learning algorithms, including LightGBM, Random Forest, and XGBoost, were employed to construct predictive models, each offering distinct methodological advantages. LightGBM, as a gradient boosting framework, is particularly efficient in handling large-scale clinical data and capturing complex nonlinear relationships. Random Forest provides robust performance through ensemble learning and is less prone to overfitting, making it suitable for heterogeneous ICU populations. XGBoost, known for its strong regularization capability and optimization efficiency, further enhances predictive accuracy and model stability. The consistent performance observed across these models strengthens the reliability of our findings and highlights the applicability of machine learning techniques in critical care prognostication.

Importantly, beyond model development, we translated the predictive framework into a web-based tool, enabling real-time, individualized risk estimation at the bedside. This tool allows clinicians to input patient-specific variables and obtain personalized mortality predictions, thereby bridging the gap between statistical modeling and practical clinical use. Compared with traditional scoring systems, such an approach offers greater flexibility, improved interpretability when combined with SHAP analysis, and the potential to support dynamic clinical decision-making.

From an innovation perspective, this study not only integrates multiple machine learning algorithms for risk prediction but also emphasizes model interpretability and clinical usability. By incorporating explainable AI techniques and deploying an accessible web interface, our approach facilitates both understanding and application of model outputs. Collectively, these features underscore the potential of combining advanced analytics with digital tools to enhance precision medicine and optimize

management strategies in critically ill patients.

Several limitations need to be considered. To begin with, due to the retrospective nature of the study design, it is not possible to infer causal relationships. Second, although multiple confounders were adjusted for, residual confounding due to unmeasured variables cannot be excluded. Third, classification based on a single cutoff may oversimplify GV heterogeneity. Fourth, GV estimation may be influenced by the frequency and timing of glucose measurements. Fifth, the ICU-based population may limit generalizability, and the single-center validation cohort had a relatively small sample size. In addition, although a machine learning model was developed, further external validation and assessment of clinical interpretability are required. Finally, the underlying biological mechanisms were not directly investigated and warrant further exploration. Further prospective investigations with larger sample sizes are warranted to confirm these results and to clarify whether strategies aimed at reducing GV may lead to improved clinical outcomes.

5.Conclusion

GV was found to be significantly linked with higher risks of both ICU and in-hospital mortality among patients undergoing colorectal cancer surgery. Notably, this association appeared to follow a roughly linear pattern across the observed range of GV, with greater variability corresponding to poorer outcomes. Dynamic glucose monitoring may improve risk stratification in this population. Machine learning models demonstrated moderate predictive performance, with Random Forest achieving the best discrimination, followed by gradient boosting models (XGBoost and LightGBM). While these ensemble models improved risk discrimination, traditional regression models better reflected survival patterns. Overall, maintaining stable glycaemic control may help improve postoperative outcomes in critically ill CRC patients.

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Author Contributions

Yuji Yan, Xinming Lei;Ming Yang; Shengshan Xu; Ke-Jie He were equally responsible for writing and revising the manuscript. Ke-Jie He offered funding support and played a role in the conception, design, editing, and supervision of the manuscript sections. All authors reviewed and agreed on the final version of the manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included either in this article.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors have declared that no conflict of interest exists.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Quzhou Affiliated Hospital of Wenzhou Medical University (Approval No.: 2026-028).Given the retrospective design and use of de-identified routinely collected clinical data, the requirement for informed consent was waived. All research procedures involving human data were

performed in accordance with the Declaration of Helsinki.

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