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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

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Abstract

Patients with gastrointestinal surgery have a higher incidence of infection-related complications than the rest of those who undergo clean cut surgery. It can lead to a worse prognosis for patients. This study aimed to assess the association between glycemic variability (GV) and postoperative infection-related complications of gastrointestinal cancer patients. A total of 438 patients were included in this study. Using univariate and multivariate regression analyses, the risk factors for postoperative complications were determined. And nomogram prediction models were constructed through machine learning. The performance of the nomogram was assessed with respect to the calibration curves. Univariate and multivariate regression analysis showed that high GV on post operation day (POD)1 ($P < .001$), high leukocytes on POD4 ($P = .003 < .01$) and alcohol consumption ($P = .005 < .01$) were independent risk factors for postoperative infection-related complications in patients with gastrointestinal cancers. The area under the curve (AUC) showed that these 3 prediction models established through logistic regression (AUC = 0.81), XGBoost (AUC = 0.82) and random forest (AUC = 0.78) all performed well. Our study confirmed that higher GV on POD1 were independent risk factors for postoperative infection-related complications within 30 days of surgery in patients with gastrointestinal cancers. And the nomogram prediction model confirmed its capable for predicting infection-related complications.

Abbreviations: AUC = area under the curve, GV = glycemic variability, POD = post operation day.

Keywords: biomarkers, gastrointestinal cancer, glycemic variability, infection-related complications, nomogram

1. Introduction

The treatment model for gastrointestinal cancers has entered the era of comprehensive therapy.[1] The addition of targeted- and immuno-therapy have greatly improved the treatment response and prognosis of patients with gastrointestinal carcinoma.[2,3] However, increased postoperative morbidity was observed in patients accepting the perioperative combination therapy.[2] These complications seriously impede the postoperative recovery. Patients with postoperative complications often require additional interventions and care, including antibiotics, peritoneal irrigation, or debridement, and even additional surgery for severe cases. Economic burden and risk of motality are higher in patients with postoperative complications.[4] Early identification

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All data generated or analyzed during this study are included in this published article (and its supplementary information files).

This retrospective study was approved by the Ethics Committee of Yantai Yuhuangding Hospital, Qingdao University, and the informed consent requirement is waived due to the retrospective nature of the study.

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enables early treatment and can limit the consequences of the postoperative complications.

The association between glycemia and postoperative complications has been confirmed in previous studies. In cases of hyperglycemia, the production of reactive oxygen species is considered a key mechanism of tissue damage, leading to inflammation, necrosis of tissues and an increased risk of infections.[5,6] Therefore, glycemic control is a crucial part of appropriate perioperative management. A growing amount of evidence suggested that increased glycemic fluctuations can cause more severe oxidative stress and cellular function impairment compared with persistent hyperglycemia.[7–9] Hospitalized patients with high glycemic variability (GV) face more than triple the risk of death.[9] For patients undergoing hematopoietic cell transplantation, those with high GV have twice the infection risk compared with patients with low GV. In addition, their infection risk is higher than that of patients with either hyperglycemia or hypoglycemia alone.[10]

At present, GV has been proved to increase the risk of infection following cardiac surgery.[11,12] But there is still a lack of studies between GV and postoperative infection-related complications of the gastrointestinal surgery. Gastrointestinal surgery, classified as potentially contaminated, inherently carries an elevated risk of surgical site infection complications.[13] In this study, we hypothesized that GV is a critical factor contributing to the increased risk of postoperative infectious complications following gastrointestinal surgery. Thus, by investigating the association between GV and postoperative infection-related complications in gastrointestinal cancer patients, we aim to assess whether GV can serve as a predictor of postoperative infections.

2. Material and method

2.1. Patient selections

We included 438 patients with gastrointestinal cancers who underwent standard radical surgery in the Department of Gastrointestinal Surgery, Yantai Yuhuangding Hospital, Qingdao University, from April 2022 to April 2024. All surgery were performed base on the guidelines of Chinese society of clinical oncology (CSCO). The inclusion criteria included: age ≥ 18 years; no obvious contraindications in preoperative examination; preoperative pathological determination of gastric or colorectal cancer; receiving R0 resection for gastrointestinal cancer; daily energy provided by parenteral nutrition at 25 to 30 kcal/kg per day after surgery; and life expectancy ≥ 6 months. The exclusion criteria are as follows: patients without a complete baseline examination; cancers with metastasis or comorbidities identified in preoperative examination requiring emergency surgery; with malignancy other than gastrointestinal cancers; have other medical conditions that may affect the results of the study; and patients with serious complications of diabetes.

Medical records were retrospectively reviewed to obtain the following clinical information: age at surgery, history of smoking, history of alcohol, history of diabetes, history of hypertension, history of cerebrovascular diseases, cancer stage. Laboratory data included leukocytes, hemoglobin, albumin, and creatinine values on postoperation day 1 (POD1) and POD4, and glycemia on POD1, POD2, and POD3.

2.2. Determination of glucose variability

All postoperative glycemia values were derived from the blood glucose detector data, and the glycemia test is at 6 am, 2 pm, and 8 pm each day. Based on the glucose value available for each patient during perioperative period, the mean and standard deviation of daily glucose value were calculated. And the GV index is defined as the coefficient of variation, which is the ratio of daily glycemic standard deviation to the daily glycemic mean.[14]

$$GV = Daily\ Glycemic\ Standard\ Deviation / Daily\ Glycemic\ Mean \times 100\%$$

2.3. Outcome measures

According to the *International Classification of Diseases, 11th Revision*, postoperative complications were extracted and analyzed from postoperation to 30 days after discharge.[15] Major complications included intraperitoneal infection, incision infection, anastomotic leakage, lung infection, urinary tract infection, fever and blood culture confirmed infection. Assessment of resource utilization, length of hospital stays, disposition of discharge, and 30-day readmission were also recorded.

2.4. Statistical analysis and development of nomogram

For continuous variables, data with correlations exceeding 0.5 were excluded to mitigate potential multicollinearity. Meanwhile, to address the potential multicollinearity in clinical practice, we also excluded GV values on POD2 and POD3. Cutoff values were determined using receiver operating characteristic curve and divided each variable into high and low groups. R and SPSS were then used to analysis. The data were divided into training and validation groups. The correlation of infection-related complications and variables in the training group was first analyzed through Fisher exact test and χ^2 test. Variables with P value <.05 were then enrolled into the multivariable analysis for identifying the independent risks for infection-related complications. Variables with P value <.01 were found as independent risk factors. Logistics regression, random forest and XGBoost were then used to establish the prediction model through, respectively.

The performance of the nomogram was assessed by discrimination and calibration. The validation group was used to validate the results obtained from training group. The credibility was determined by the area under curve (AUC). The calibration of the prediction model was evaluated by calibration curves and Hosmer-Lemeshow tests.[16]

3. Results

3.1. Patient features

A total of 438 patients undergoing radical surgery for gastrointestinal cancer were included in the study with 308 patients in training group and 130 patients in validation group. There were no differences between groups regarding age, BMI, postoperative GV etc. The comparisons between the training group and validation group are summarized in Table 1.

Among the included patients, there were 42 patients with infection-related complications, of which 8 had intraperitoneal infection, 10 had anastomotic leakage, 5 had incision infection, 9 had lung infection, 1 had urinary tract infection, 7 had fever, 1 had blood culture confirmed infection, and 2 patients had anastomotic leakage after discharge and returned to the hospital for secondary surgeries.

3.2. Association between postoperative infection-related complications and GV

First, considering for the potential multicollinearity, we excluded GV values on POD2 and POD3, Hgb on POD4, Albumin on POD4 and Creatinine on POD4 (Fig. 1). In univariate analysis, we found that GV values on POD1 (P < .001), leukocytes on POD4 (P < .001) and history of alcohol (P = .003) were all

Table 1

Base line between training group and validation group.

Variables	Total (n = 438)	Training group (n = 308)	Validation group (n = 130)	*P*
Complication, n (%)				1
No	396 (90.41)	278 (90.26)	118 (90.77)	
Yes	42 (9.59)	30 (9.74)	12 (9.23)	
Sexual, n (%)				.276
Female	160 (36.53)	107 (34.74)	53 (40.77)	
Male	278 (63.47)	201 (65.26)	77 (59.23)	
Diabetes, n (%)				.327
No	348 (79.45)	249 (80.84)	99 (76.15)	
Yes	90 (20.55)	59 (19.16)	31 (23.85)	
History of hypertension, n (%)				.703
No	272 (62.1)	189 (61.36)	83 (63.85)	
Yes	166 (37.9)	119 (38.64)	47 (36.15)	
History of alcohol, n (%)				.755
No	356 (81.28)	252 (81.82)	104 (80)	
Yes	82 (18.72)	56 (18.18)	26 (20)	
History of smoke, n (%)				.992
No	332 (75.8)	234 (75.97)	98 (75.38)	
Yes	106 (24.2)	74 (24.03)	32 (24.62)	
History of cerebrovascular disease, n (%)				.43
No	412 (94.06)	292 (94.81)	120 (92.31)	
Yes	26 (5.94)	16 (5.19)	10 (7.69)	
History of heart disease, n (%)				.48
No	399 (91.1)	283 (91.88)	116 (89.23)	
Yes	39 (8.9)	25 (8.12)	14 (10.77)	
Type of cancer, n (%)				.078
Gastric cancer	204 (46.58)	137 (44.48)	67 (51.54)	
Colon cancer	120 (27.4)	94 (30.52)	26 (20)	
Rectal cancer	114 (26.03)	77 (25)	37 (28.46)	
Tumor classification, n (%)				.835
1	64 (14.61)	45 (14.61)	19 (14.62)	
2	64 (14.61)	47 (15.26)	17 (13.08)	
3	226 (51.6)	160 (51.95)	66 (50.77)	
4a	84 (19.18)	56 (18.18)	28 (21.54)	
Node classification, n (%)				.518
0	221 (50.46)	159 (51.62)	62 (47.69)	
1	110 (25.11)	75 (24.35)	35 (26.92)	
2	71 (16.21)	52 (16.88)	19 (14.62)	
3	36 (8.22)	22 (7.14)	14 (10.77)	
Metabolism classification, n (%)				.54
0	425 (97.03)	300 (97.4)	125 (96.15)	
1	13 (2.97)	8 (2.6)	5 (3.85)	
Age, median (Q1, Q3)	66 (59, 72)	66.5 (59, 72)	65 (59, 73)	.678
BMI, median (Q1, Q3)	22.5 (20.6, 25.48)	22.55 (20.8, 25.5)	22.3 (20.6, 25.2)	.449
Leukocytes on POD1, n (%)				.656
≤13.79	374 (85.39)	265 (86.04)	109 (83.85)	
>13.79	64 (14.61)	43 (13.96)	21 (16.15)	
Leukocytes on POD4, n (%)				.114
≤8.075	298 (68.04)	202 (65.58)	96 (73.85)	
>8.075	140 (31.96)	106 (34.42)	34 (26.15)	
GV on POD1, n (%)				.542
≤0.211	264 (60.27)	189 (61.36)	75 (57.69)	
>0.211	174 (39.73)	119 (38.64)	55 (42.31)	
Hgb on POD1, n (%)				.512
≤105.50	117 (26.71)	79 (25.65)	38 (29.23)	
>105.50	321 (73.29)	229 (74.35)	92 (70.77)	
Albumin on POD1, n (%)				.317
≤35.35	307 (70.09)	211 (68.51)	96 (73.85)	
>35.35	131 (29.91)	97 (31.49)	34 (26.15)	
Creatinine on POD1, n (%)				.437
≤52.50	135 (30.82)	91 (29.55)	44 (33.85)	
>52.50	303 (69.18)	217 (70.45)	86 (66.15)	

GV = glycemic variability, POD = post operation day.

Table 2

Comparison of whether complications occur in the training set.

Variables	Total (n = 308)	No (n = 278)	Yes (n = 30)	*P*
Sexual, n (%)				.71
Female	107 (34.74)	98 (35.25)	9 (30)	
Male	201 (65.26)	180 (64.75)	21 (70)	
Diabetes, n (%)				.392
No	249 (80.84)	227 (81.65)	22 (73.33)	
Yes	59 (19.16)	51 (18.35)	8 (26.67)	
History of hypertension, n (%)				.72
No	189 (61.36)	172 (61.87)	17 (56.67)	
Yes	119 (38.64)	106 (38.13)	13 (43.33)	
History of alcohol, n (%)				.003
No	252 (81.82)	234 (84.17)	18 (60)	
Yes	56 (18.18)	44 (15.83)	12 (40)	
History of smoke, n (%)				.054
No	234 (75.97)	216 (77.7)	18 (60)	
Yes	74 (24.03)	62 (22.3)	12 (40)	
History of cerebrovascular disease, n (%)				.058
No	292 (94.81)	266 (95.68)	26 (86.67)	
Yes	16 (5.19)	12 (4.32)	4 (13.33)	
History of heart disease, n (%)				.722
No	283 (91.88)	256 (92.09)	27 (90)	
Yes	25 (8.12)	22 (7.91)	3 (10)	
Type of cancer, n (%)				.646
Gastric cancer	137 (44.48)	126 (45.32)	11 (36.67)	
Colon cancer	94 (30.52)	84 (30.22)	10 (33.33)	
Rectal cancer	77 (25)	68 (24.46)	9 (30)	
Tumor classification, n (%)				.6
1	45 (14.61)	40 (14.39)	5 (16.67)	
2	47 (15.26)	41 (14.75)	6 (20)	
3	160 (51.95)	144 (51.8)	16 (53.33)	
4a	56 (18.18)	53 (19.06)	3 (10)	
Node classification, n (%)				.081
0	159 (51.62)	137 (49.28)	22 (73.33)	
1	75 (24.35)	71 (25.54)	4 (13.33)	
2	52 (16.88)	50 (17.99)	2 (6.67)	
3	22 (7.14)	20 (7.19)	2 (6.67)	
Metabolism classification, n (%)				1
0	300 (97.4)	270 (97.12)	30 (100)	
1	8 (2.6)	8 (2.88)	0 (0)	
Age, median (Q1, Q3)	66.5 (59, 72)	66 (59, 72)	68.5 (61.5, 73)	.305
BMI, median (Q1, Q3)	22.55 (20.8, 25.5)	22.5 (20.7, 25.5)	22.7 (21.9, 25.4)	.372
Leukocytes on POD1, n (%)				.587
≤13.79	265 (86.04)	240 (86.33)	25 (83.33)	
>13.79	43 (13.96)	38 (13.67)	5 (16.67)	
Leukocytes on POD4, n (%)				<.001
≤8.075	202 (65.58)	191 (68.71)	11 (36.67)	
>8.075	106 (34.42)	87 (31.29)	19 (63.33)	
GV on POD1, n (%)				<.001
≤0.211	189 (61.36)	181 (65.11)	8 (26.67)	
>0.211	119 (38.64)	97 (34.89)	22 (73.33)	
Hgb on POD1, n (%)				.334
≤105.50	79 (25.65)	74 (26.62)	5 (16.67)	
>105.50	229 (74.35)	204 (73.38)	25 (83.33)	
Albumin on POD1, n (%)				.207
≤35.35	211 (68.51)	194 (69.78)	17 (56.67)	
>35.35	97 (31.49)	84 (30.22)	13 (43.33)	
Creatinine on POD1, n (%)				.319
≤52.50	91 (29.55)	85 (30.58)	6 (20)	
>52.50	217 (70.45)	193 (69.42)	24 (80)	

GV = glycemic variability, POD = post operation day.

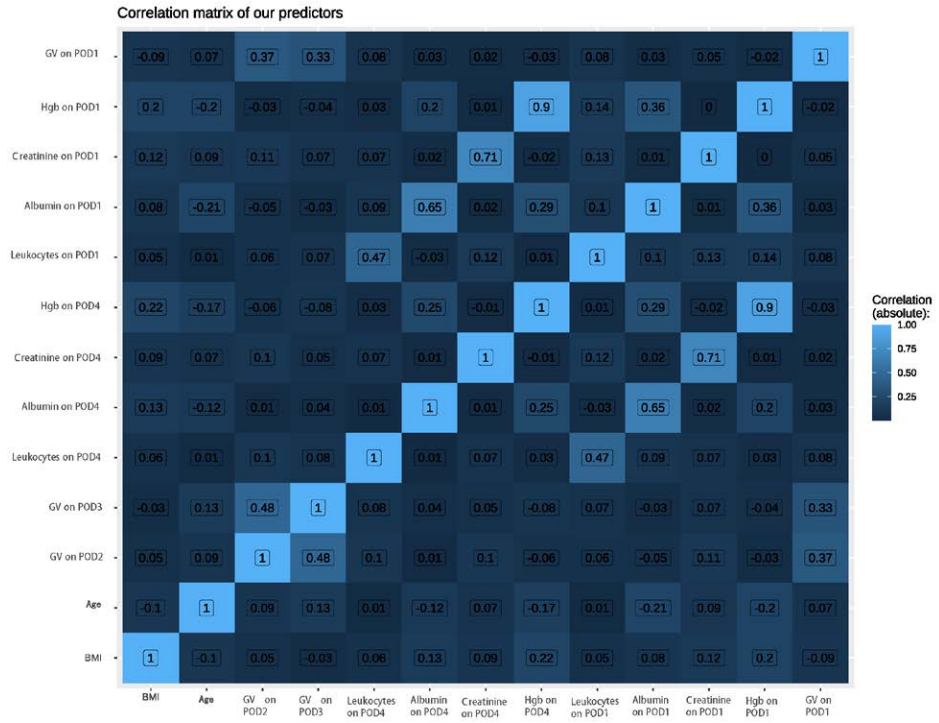

Figure 1. Correlation between our predictors. GV = glycemic variability, POD = post operation day.

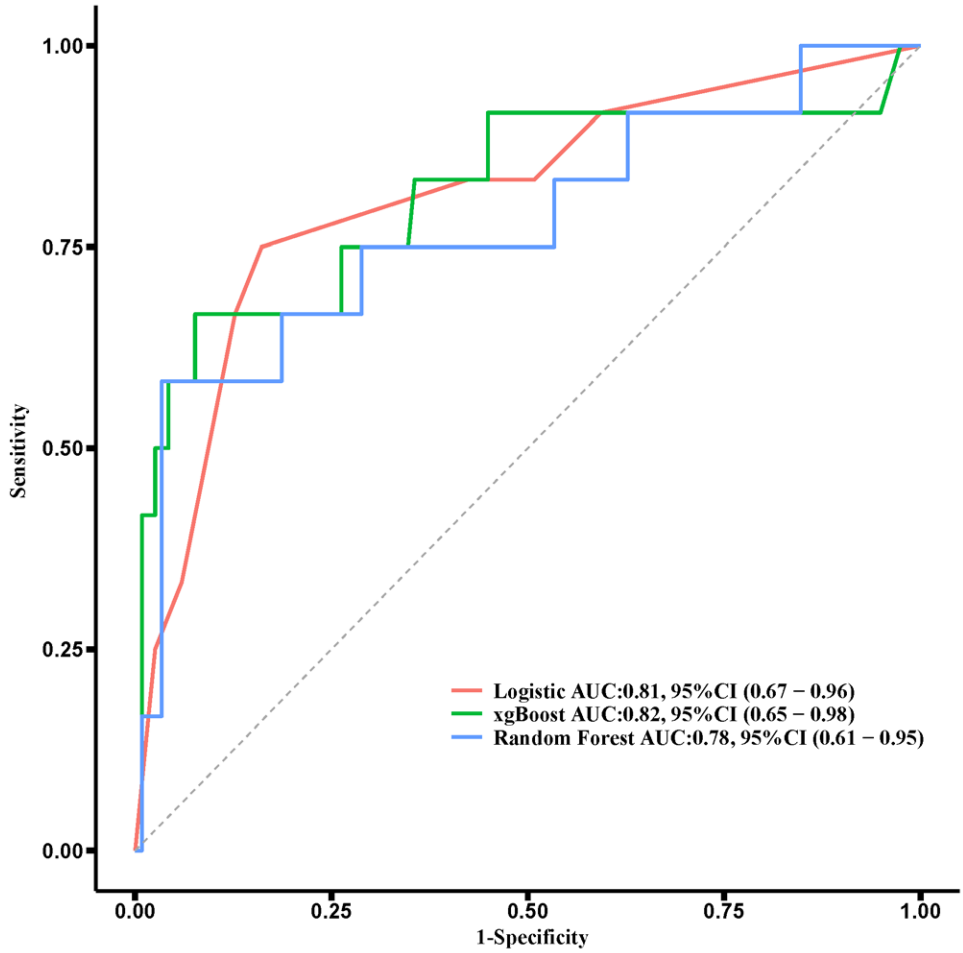

Figure 2. Comparison of ROC cure between prediction model of Logistic regression, Random forests and XGBoost. AUC = area under the curve, ROC = receiver operating characteristic.

associated with postoperative infection-related complications, while diabetes ($P = .392$) and leukocytes on POD1 ($P = .851$) has no effect on the occurrence of postoperative infection-related complications (Table 2). Further multivariate risk regression analysis showedthat GV on POD1 ($P < .001$, OR, 5.459 [2.263–13.165]), leukocytes on POD4 ($P = .003$, OR, 3.490 [1.526–7.985]) and a history of alcohol consumption ($P = .005$, OR, 3.495 [1.458–8.380]) were all independent risk factors for postoperative infection-related complications in patients undergoing radical surgery for gastrointestinal cancer (Table 3).

3.3. Development and validation of nomogram

To further investigate the potential of these 3 risk factors in predicting postoperative infection-related complications in gastrointestinal cancers, we developed prediction models using 3 distinct methods: logistic regression, XGBoost, and random forest. The receiver operating characteristic curve analysis indicated that there were no significant differences in the performance of these models, as evidenced by their respective area under the curve (AUC) values (AUC = 0.81, AUC = 0.82, and AUC = 0.78, respectively) (Fig. 2). Based on the results of multivariate risk regression analysis, we developed related nomogram (Fig. 3A). The calibration curve and Decision Curve Analysis (DCA) depicted in Figure 3B, 3C, and 3D demonstrate that the logistic model exhibits a good fit and fciliates clinical decision-making. In the ranking of feature importance for the random forest and XGBoost models on the training data, the variable GV on POD1 ranks 3rd and 2nd, respectively, while leukocytes on POD4 rank 4th and 3rd, respectively (Fig. 4).

4. Discussion

GV refers to the unstable state where blood glucose levels fluctuate between peaks and troughs, due to insulin resistance.[14] There is still debate over whether GV or blood glucose level control should be prioritized. Recent studies about GV focused on its increased risk of postoperative morbidity, leading to prolonged hospital stays, worsened disease outcomes, and increased mortality in hospitalized patients.[17,18] Monitoring of glucose levels is essential to patient management during perioperative period, and GV were easier to obtain. In clean surgeries, patients with high GV experience more than twice the risk of postoperative infections compared with those with low GV.[19]

Table 3

Multivariate regression analysis.

	Estimate	SE	Wald χ^2	*P*	OR	Lower	Upper
Intercept	−4.065	0.476	−8.545	<.001	0.017	0.007	0.044
GV on POD1, >0.211	1.697	0.449	3.779	<.001	5.459	2.263	13.165
Leukocytes on POD4, >8.075	1.250	0.422	2.960	.003	3.490	1.526	7.985
History of alcohol, Yes	1.251	0.446	2.805	.005	3.495	1.458	8.380

GV = glycemic variability, POD = post operation day.

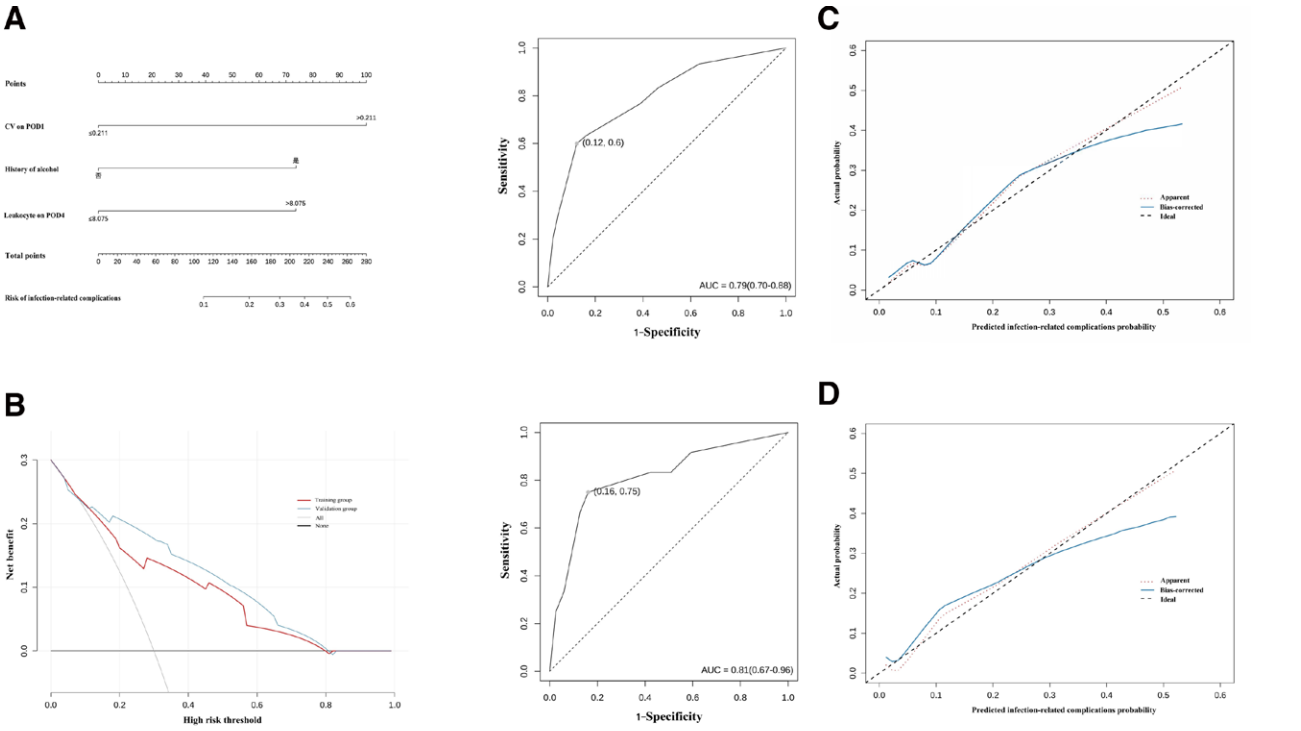

Figure 3. Nomogram, DAC curve, ROC curve and Calibration curve for the prediction of infection-related complications. AUC = area under the curve, POD = post operation day, ROC = receiver operating characteristic.

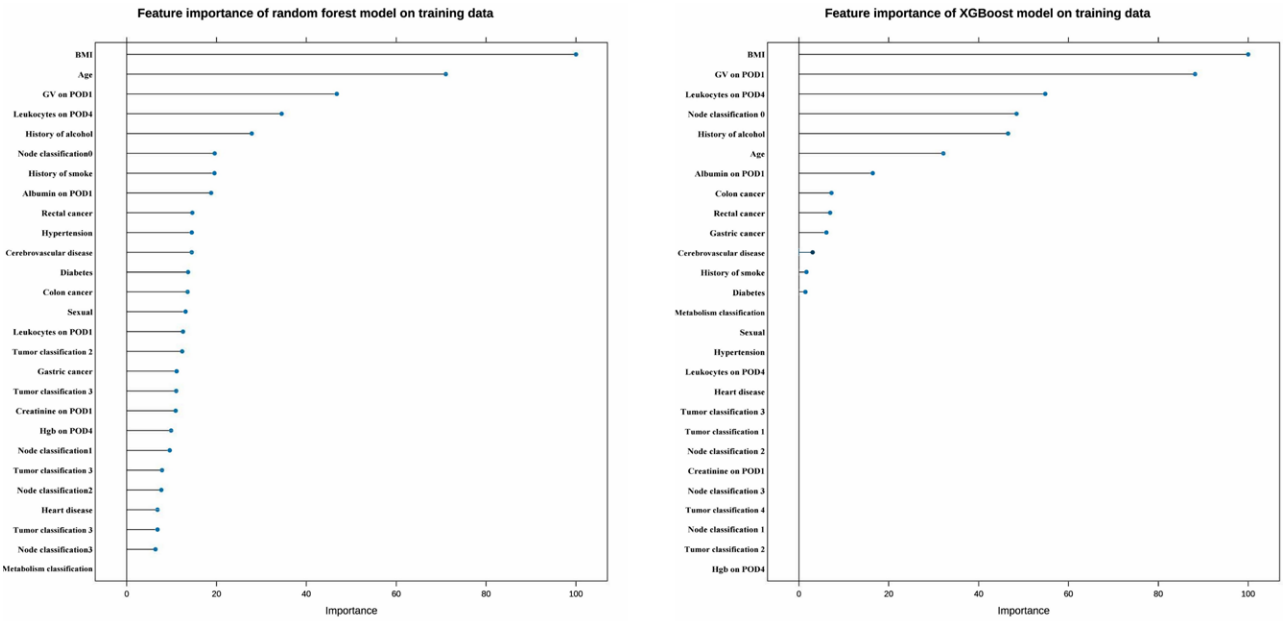

Figure 4. the feature importance of random forest model and XGBoost model on training data. GV = glycemic variability, POD = post operation day.

Mechanistically, higher GV can affect the immune system and metabolism, activate pro-inflammatory cascades, and exacerbate postoperative oxidative stress, which cause more serious harm than continuous hyperglycemia and hypoglycemia alone. Our findings indicate that patients with higher GV on POD1 were more likely to experience infection-related complications. In addition, we established a predictive model using machine learning algorithms, to confirm the reliability of GV on POD1 in predicting postoperative complications.

Concomitant insulin resistance occurs during postoperative period, leading to elevated infection rates, especially in patients undergoing heart surgery or suffering from burn injuries.[20,21] In patients receiving enteral and parenteral nutritional intervention, glucose control frequently accompanied by hyperglycemia and hypoglycemia, which can impede tissue healing.[22–24] For patients undergoing gastrointestinal surgery, short-term fasting and parenteral nutrition support are necessary, and in turn, GV and blood glucose levels become more difficult to maintain within the normal range.[25] Therefore, it is crucial to determine whether to prioritize managing GV or blood glucose levels. Our study confirmed that high GV is a risk factor for postoperative infection-related complications in patients undergoing radical gastrointestinal surgery. These factors elevate the stress levels and promote the secretion of insulin-antagonistic hormones, causing glucose metabolism disorders. To cope with these recovery barriers, enhanced recovery after surgery protocols were applied to reduce surgical stress, accelerate patient recovery, and improve prognosis through effective and reasonable modifications to the treatment process. However, enhanced recovery after surgery management cannot completely eliminate the impact of surgery on patients.[26] Our study confirmed that the recognition and intervention of insulin resistance may help reduce the incidence and severity of postoperative infections.

GV are recommended to be controlled below 0.36 in patients with diabetes mellitus.[27] However, in our results, the median GV on POD1 in patients with infection-related complications is merely 0.211, which is similar to previous report on association between GV and complications.[19] Our results also indicated that the cutoff valve of GV need to be realigned to recognize the subgroup with higher infection risk. Surgery-related stress was considered to account for the immune function impairment, metabolic disorder, and poor glucose control, leading to a higher incidence of infection-related complications.[28] Therefore, we recommended that the patients with GV exceeding 0.211 require enhanced surveillance after gastrointestinal surgery to acquire the early detection of infection-related complications.

Although most patients experienced a transient increase in leukocytes on PDO1, no correlation were observed between this transient increase and postoperative infection-related complications. Increased leukocytes on PDO1 are induced by caused by surgical stress, acting as immune system activation and self-protection mechanism to reduce postoperative infection risk.[29,30] In contrast, patients with persistent leukocyte elevation are often considered high-risk for infection.[31] In our study, elevated leukocytes on POD4 were related to infection-related complications. In addition, a history of alcohol consumption was associated with postoperative infection-related complications, as alcohol abuse is a known risk factor for complications in gastrointestinal surgery. Long-term alcohol intake can damage the immune system and delay wound healing, leading to a nearly double risk of postoperative infection.[32,33]

There are limitations to our research. First, as a single-center retrospective study, there could be selection bias, limiting the applicability of our model to other hospitals. Further prospective studies are needed to corroborate our findings. In addition, excluding patients with incomplete glycemia or other data might have led to selection bias and affected the final predictions.

5. Conclusion

Our study confirms that higher GV on POD1 is an independent risk factor for postoperative infection-related complications in patients with gastrointestinal cancers. This finding provides a new opportunity for predicting and intervening in postoperative infection-related complications. Furthermore, we established a relevant risk nomogram prediction model that may help clinicians identify high-risk groups for infection-related complications following gastrointestinal surgery.

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