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Original Article

Effects of T2DM on postoperative outcome of patients with colorectal cancer: a study on the relationship between blood glucose control and survival rate

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Abstract: To investigate the impact of type 2 diabetes (T2DM) on the prognosis of colorectal cancer (CRC). The data of 312 patients with CRC treated in the First Affiliated Hospital of Huzhou University from 2012 to 2018 were analyzed retrospectively. The patients were divided into a comorbidity group (n = 62) and a non-comorbidity group (n = 250) according to the presence of T2DM. The baseline data of the two groups were balanced by 1:2 propensity score matching (PSM). Kaplan-Meier analysis and Log-rank test were employed to compare the 5-year overall survival (OS) rates of patients. Cox regression model and inverse probability of treatment weighting (IPTW) were utilized to assess the influence of T2DM on 5-year OS of patients. Based on the results of Cox regression, a nomogram model of T2DM on 5-year OS of patients was constructed. A total of 62 patients in the comorbidity group and 124 patients in the non-comorbidity group were matched using PSM. The 5-year OS rate was lower in the comorbidity group than in the non-comorbidity group (82.23% VS 90.32%, $P = 0.038$). Subgroup analysis showed that the 5-year overall survival rate was higher in the good blood glucose control group than in the poor blood glucose control group (97.14% VS 62.96%, $P<0.01$). Multivariate Cox regression showed that the 5-year mortality risk in the comorbidity group was 2.641 times higher than that in the non-comorbidity group ($P = 0.026$). IPTW analysis showed that the 5-year risk of death in the comorbidity group was 2.458 times that of the non-comorbidity group ($P = 0.019$). The results showed that poor blood glucose control, BMI≥25 kg/m^2, low differentiation, III/IV stage, and postoperative infection were independent factors affecting the 5-year overall survival rate of CRC patients ($P<0.05$). The ROC curve showed that the AUCs of the constructed model in predicting the 5-year OS in the training set and the testing set were 0.784 and 0.776, respectively. T2DM is identified as a risk factor for reduced 5-year survival among CRC patients, necessitating increased attention for this subgroup, particularly those with poor blood glucose control.

Keywords: Colorectal cancer, type 2 diabetes, survival, blood glucose

Introduction

Colorectal cancer (CRC) is a common malignant tumor of the digestive system with high morbidity and mortality. According to the report of GLOBOCAN 2020, the number of new CRC cases worldwide was 1.93 million and about 940,000 deaths worldwide, accounting for 10% and 9.4% of the incidence and death of malignant tumors worldwide, respectively [1]. China is a country with a high incidence of cancer, according to the data of the National Cancer Center in 2022, the incidence and mortality rates of CRC ranked fourth and fifth among male patients, while third and fourth among female patients, respectively [2]. Due to the lack of early symptoms and early screening system, as well as limited public awareness [3], the proportion of patients with advanced CRC in China is still high [4], which has brought great

challenges to the prevention and control of CRC. Diabetes mellitus (DM) is a typical metabolic disease characterized by persistent hyperglycemia and insulin resistance [5]. With the improvement of social living standards, the prevalence of diabetes is increasing year by year. According to the diagnostic criteria of the American Diabetes Association, the total prevalence of diabetes in mainland China reached 12.8% in 2017, of which type 2 diabetes mellitus (T2DM) accounted for more than 90% and continued to grow [6]. In recent years, study evidence has shown an increase in the incidence of certain cancers in T2DM patients, including CRC [7-9]. In addition, a study has found the cancer mortality associated with T2DM has also increased [10]. Despite the potential for improving cancer outcomes by managing T2DM, there is limited research on the relationship between T2DM and CRC prognosis, particularly concerning postoperative survival rates in CRC patients. Given this, this study aims to explore this area to aid the diagnosis and treatment of CRC.

Materials and methods

Patient characteristics

The clinical data of 312 patients with CRC treated in the First Affiliated Hospital of Huzhou University from January 2012 to January 2018 were retrospectively collected. Inclusion criteria: (1) Patients who were confirmed with colon cancer and rectal cancer by imaging examination and pathological diagnosis; (2) Patients who underwent radical surgery; (3) Patients with detailed clinical data. Exclusion criteria: (1) Patients comorbid with other malignant tumors; (2) Patients with advanced intestinal cancer, irritable bowel syndrome or another enteritis who received conservative treatment; (3) Patients with systemic infection. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Huzhou University.

Data collection

The general data of patients collected from the hospital medical record system included age, sex, body mass index (BMI), history of hypertension, and duration of hospital stay. Pathological information included tumor location, histological type, maximum tumor diameter, differentiation degree, and TNM stage. Operation-related information included surgical regimen, intraoperative blood loss, postoperative chemotherapy, postoperative infection, etc.

Evaluation of T2DM and glucose control

For assessing type 2 diabetes mellitus (T2DM) and its management, the criteria used were based on a 24-hour blood glucose screening upon admission [11], defined as follows: (1) T2DM is defined as the random plasma glucose (RPG) level ≥7.0 mmol/L after a fasting period of at least 8 hours; (2) Good control of T2DM is defined as fasting RPG between 7.0 mmol/L and 11.1 mmol/L; (3) Poor control of T2DM is defined as fasting RPG >11.0 mmol/L.

Continuous blood glucose monitoring was conducted at a frequency of 1 measurement per hour until stabilization of glucose levels. Based on individual's initial blood glucose levels, varying doses of insulin were administered subcutaneously to maintain blood glucose within the predetermined target range. After achieving stable control, monitoring frequency was reduced to every three hours, with insulin doses adjusted accordingly to maintain optimal glycemic control. In instances of lower-than-expected glucose levels, slow intravenous administration of glucose was employed for adjustment purposes while maintaining hourly blood glucose monitoring.

Follow-up survey

Survival data for patients was obtained from electronic medical records, outpatient follow-up records, and regular follow-up telephone information. Telephone follow-ups were conducted at 3rd, 6th, 9th, and 12th month after the operation, followed by every 4 months from the second year to the fifth year. The follow-up ended in February 2023. The primary outcome was 5-year overall survival (OS), defined as the time from treatment initiation to either the last follow-up or death.

Statistical analyses

Propensity score matching (PSM) was performed using R 4.2.3, employing both nearest neighbor matching method and caliper matching method, with a caliper set at 0.2. Meaningful indicators identified through single-factor analysis were matched in a ratio of 1:2.

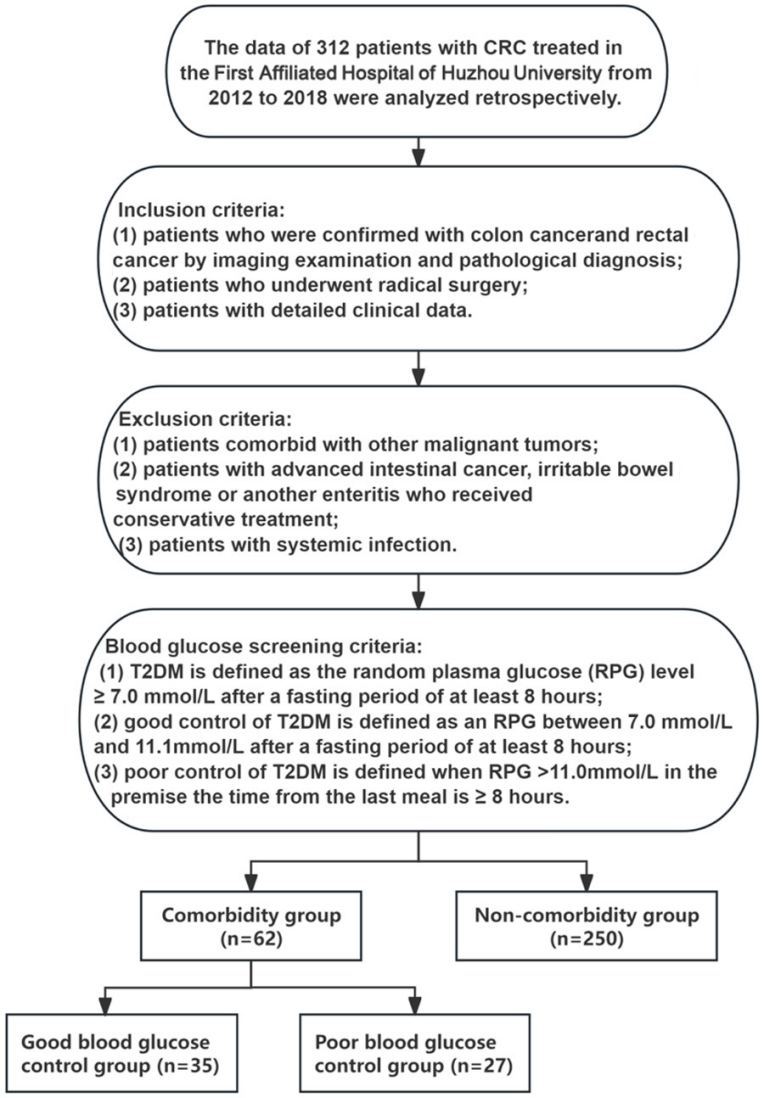

Figure 1. Flowchart. T2DM, type 2 diabetes mellitus.

The data were preprocessed and analyzed using SPSS 26.0 software. Quantitative data conforming to normal distribution were presented as the mean ± standard variance ($\bar{x} \pm s$), and an independent sample t-test was adopted for inter-group comparison. Counting data were expressed by numbers and rate [n (%)] and analyzed using the chi-square test. The Kaplan-Meier method and Log-rank test were employed to compare the 5-year OS rate between the two groups. The Cox regression model and inverse probability of treatment weighting (IPTW) model were utilized to analyze the factors influencing CRC prognosis, while a nomogram prediction model was constructed. $P<0.05$ was considered with statistical significance.

According to the random number generated by the computer, 312 patients were divided into a training set and a testing set according to a ratio of 7:3. The training set was used to establish the model, and the testing set was used to verify the effectiveness of the model. Based on the results of multivariate Cox regression analysis, a nomogram model for the 5-year OS rate of CRC patients was constructed using R 4.2.3, and the predictive ability of the ROC curve analysis model was used.

Results

Sample screening

Based on predefined inclusion criteria, a total of 445 eligible samples were collected in this study. Subsequently, according to the exclusion criteria, 312 samples were finally screened. Among them, 62 T2DM patients were divided into the comorbidity group, and the rest 250 patients were classified into the non-comorbidity group. Furthermore, based on blood glucose control levels, patients with T2DM were categorized into the good blood glucose control group (n = 35) or the poor blood glucose control group (n = 27). The inclusion and exclusion criteria were visually represented in a flow chart for enhanced clarity (**Figure 1**).

Comparison of clinical data between the two groups

Statistical differences in BMI, surgical regimen, intraoperative blood, postoperative infection, and duration of hospital stay were observed between the comorbidity group and the non-comorbidity group; however, no statistical differences in age, sex, history of hypertension,

Table 1. Comparison of clinical data between the two groups [n (%)]

Data	Comorbidity group (n = 62)	Non-comorbidity group (n = 250)	x^2	P
Age			0.204	0.652
≥60 years	27	101		
<60 years	35	149		
Sex			0.001	0.984
Male	41	165		
Female	21	85		
Body mass index			7.937	0.005
≥25 kg/m^2	19	38		
<25 kg/m^2	43	212		
History of hypertension			1.755	0.185
Yes	16	45		
No	46	205		
Tumor location			1.556	0.212
Colon	28	135		
Rectum	34	115		
Histological type			1.097	0.295
Adenocarcinoma	56	213		
Mucinous adenocarcinoma	6	37		
Maximum tumor diameter			0.404	0.525
≥4 cm	37	138		
<4 cm	25	112		
Differentiation Degree			1.793	0.181
Medium + High differentiation	57	240		
Low differentiation	5	10		
TNM stage			0.826	0.364
I + II	30	145		
III + IV	32	105		
Surgical style			1.161	0.281
Open	30	140		
Laparoscopic	32	110		
Intraoperative blood loss			4.179	0.041
≥300 mL	19	47		
<300 mL	43	203		
Postoperative chemotherapy			0.928	0.335
Yes	32	112		
No	30	138		
Postoperative infection			8.954	0.003
Yes	16	25		
No	46	225		
Hospital stay			15.228	<0.001
≥30 days	36	75		
<30 days	26	175		

TNM, tumor, node, metastasis.

tumor location, histological type, maximum tumor diameter, differentiation degree, TNM stage, surgical style, and postoperative chemotherapy (all $P>0.05$), as shown in **Table 1**.

Comparison of clinical data between the two groups after PSM

After PSM, 124 cases in the non-comorbidity group and 62 cases in the comorbidity group were successfully matched. There were no significant differences in clinical data between the two groups (P>0.05, **Table 2**).

Comparison of survival between the two groups

The 5-year OS rate of the comorbidity group was 82.23% (51/62). The 5-year OS rate of the non-comorbidity group was 94.40% (236/250) and 90.32% (112/124) before and after PSM, respectively. The 5-year OS rate was found to be higher in the non-comorbidity group compared to the comorbidity group, both before and after PSM (x^2 = 11.580/4.293, P<0.001/0.038). See **Figure 2**.

The subgroup analysis revealed that the 5-year OS rate of the good blood glucose control group was 97.14% (34/35), whereas it was 62.96% (17/27) for the poor blood glucose control group. The good blood glucose control group exhibited a significantly higher 5-year OS rate compared to those in the poor blood glucose control group (x^2 = 12.860, P<0.001). See **Figure 3**.

Influence of blood glucose on 5-year OS rate in patients with CRC

The death of CRC patients within 5 years (0 = no, 1 = yes) was used as the dependent variable, and the presence of T2DM (0 = no, 1 = yes) was used as the independent variable. After PSM, univariate Cox regression analysis showed that the 5-year mortality risk of the comorbidity group was 2.275 times that of the non-comorbidity group [HR = 2.275 (1.022-5.067), P = 0.044]. Multivariate Cox regression results showed that the 5-year mortality risk of the comorbidity group was 2.641 times that of the non-comorbidity group [HR = 2.641 (1.125-6.202), P = 0.026]. IPTW analysis showed that the 5-year mortality risk of the comorbidity group was 2.458 times that of the non-comorbidity group [HR = 2.458 (1.159-5.213), P = 0.019], which was similar to the results of multivariate Cox regression analysis. See **Table 3**.

Factors influencing the 5-year overall survival rate of CRC patients

Univariate Cox regression analysis showed that blood glucose situation, BMI, differentiation degree, TNM stage, intraoperative blood loss, postoperative infection, and hospital stay affected the 5-year OS rate of CRC patients (**Table 4**). The above factors were included as independent variables in multivariate Cox regression analysis (the assignment is shown in **Table 5**). The results showed that poor blood glucose control [HR = 2.233 (1.385-3.599), P = 0.001], BMI≥25 kg/m^2 [HR = 2.484 (1.063-5.808), P = 0.036], low differentiation [HR = 3.370 (1.208-9.399), P = 0.020], III/IV stage [HR = 3.038 (1.077-8.565), P = 0.036], and postoperative infection [HR = 2.671 (1.030-6.924), P = 0.043] were independent factors affecting the 5-year OS rate of CRC patients (**Table 6**).

A predictive model for 5-year OS of CRC patient

Based on the results of multivariate Cox regression analysis, a nomogram model of 5-year OS rate of CRC patients was constructed with blood glucose situation, BMI, differentiation degree, TNM stage, and postoperative infection as predictors (**Figure 4**). Among them, poor blood glucose control had the greatest impact on the 5-year OS rate of CRC patients, followed by low differentiation, postoperative infection, III/IV stage, and BMI≥25 kg/m^2. The ROC curve showed that the AUC of the model in predicting 5-year OS in training set and the testing set were 0.784 and 0.776, respectively (**Figure 5**).

Discussion

Although the awareness of CRC is gradually improving, the specific situation of CRC patients with T2DM has not received sufficient attention [12]. The complex metabolic changes caused by T2DM may have an important impact on the postoperative outcome of CRC patients, yet a thorough analysis and deeper understanding of these impacts are still very lacking [13]. In T2DM patients, the risk of postoperative complications and the specific impact of blood glucose control level on survival are not clear [14], which challenges medical professionals in implementing treatment decisions,

Table 2. Comparison of clinical data between two groups after PSM [n (%)]

Data	Comorbidity group (n = 62)	Non-comorbidity group (n = 124)	x^2	P
Age			0.402	0.526
≥60 years	27	48		
<60 years	35	76		
Sex			0.001	0.999
Male	41	82		
Female	21	42		
Body mass index			0.013	0.911
≥25 kg/m^2	19	39		
<25 kg/m^2	43	85		
History of hypertension			1.019	0.313
Yes	16	24		
No	46	100		
Tumor location			1.302	0.254
Colon	28	67		
Rectum	34	57		
Histological type			0.412	0.521
Adenocarcinoma	56	108		
Mucinous adenocarcinoma	6	16		
Maximum tumor diameter			0.879	0.348
≥4 cm	37	65		
<4 cm	25	59		
Differentiation Degree			0.001	0.999
Medium + High differentiation	57	115		
Low differentiation	5	9		
TNM stage			0.043	0.836
I + II	30	62		
III + IV	32	62		
Surgical style			0.043	0.836
Open	30	62		
Laparoscopic	32	62		
Intraoperative blood loss			0.334	0.564
≥300 mL	19	33		
<300 mL	43	91		
Postoperative chemotherapy			0.387	0.534
Yes	30	66		
No	32	58		
Postoperative infection			1.314	0.252
Yes	16	23		
No	46	101		
Hospital stay			0.174	0.676
≥30 days	36	68		
<30 days	26	56		

PSM, propensity score matching.

especially in preoperative and postoperative management.

In this study, statistical differences in BMI, surgical regimen, intraoperative blood loss, post-

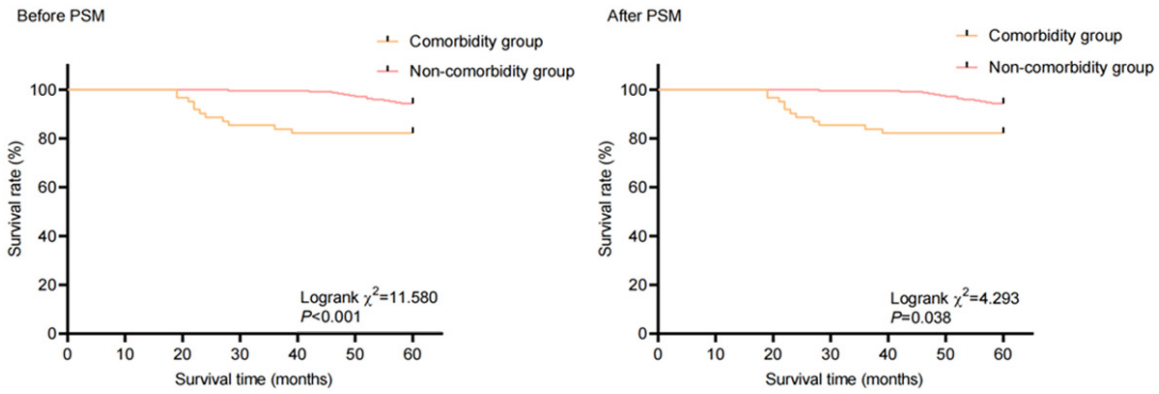

Figure 2. Comparison of 5-year overall survival rate between the comorbidity group and the non-comorbidity group before and after PSM. PSM, propensity score matching.

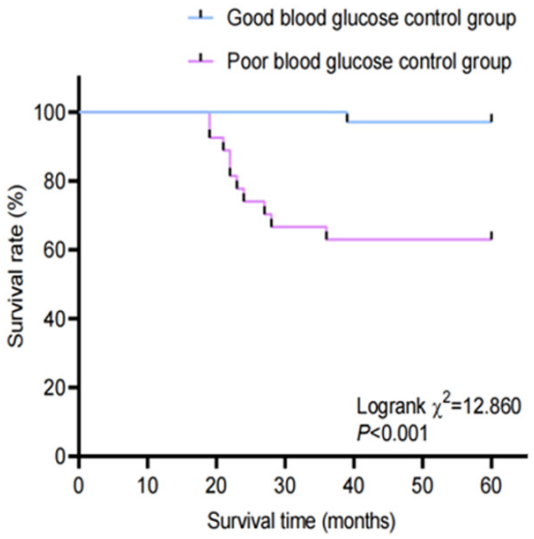

Figure 3. Comparison of 5-year overall survival rate between the good blood glucose control group and the poor blood glucose control group.

operative infection, and duration of hospital stay were observed between the comorbidity group and the non-comorbidity group. Considering the unbalance of confounding factors between groups, the PSM of 1:2 was used to balance the differences between groups to reduce the deviation of the estimation of effects. After PSM, 62 cases in comorbidity group and 164 cases in non-comorbidity group were successfully matched. There was no statistical significance in clinical data between the comorbidity group and the non-comorbidity group, and the 5-year OS rate was significantly higher in the non-comorbidity group compared to the comorbidity group. Further subgroup analysis revealed that the 5-year OS rate of the good blood glucose control group was higher than that of the poor blood glucose control group. In addition, both multifactor Cox regression and TPTW confirmed that combined T2DM was a risk factor for 5-year mortality in patients with CRC. Ottaiano et al. [15] studied the relationship between T2DM and the prognosis of metastatic CRC and found that CRC patients with T2DM had more lymph node metastasis and more distant organ involvement than patients with CRC alone. Another study [16] pointed out that although T2DM does not increase the incidence of late CRC and cancer-specific mortality of CRC patients, it does increase the all-cause mortality of CRC patients, suggesting that CRC patients with T2DM are more likely to die from other causes. T2DM is a metabolic disease characterized by the dysfunction of islet beta cells. Its basic features include insulin resistance, hyperinsulinemia, and hyperglycemia, which are crucial in cancer progression, especially CRC. Insulin resistance exists throughout T2DM, and the resulting hyperinsulinemia plays a significant role in the proliferation of cancer cells. In addition, the underlying mechanisms involved may also include inflammatory responses and exogenous pancreatitis, as noted in studies by Shimasu et al. [17, 18].

In order to further determine the prognostic factors of patients with CRC, multivariate Cox regression analysis of 312 patients showed that poor blood glucose control, BMI≥25 kg/m^2, low differentiation, III/IV stage, and postoperative infection were independent factors affecting the 5-year OS rate of patients with CRC. Poor blood sugar control can lead to

Table 3. Cox regression analysis of blood glucose on 5-year overall survival rate in CRC patients

Analytical methods	5-year overall survival rate	
	HR (95% CI)	P
Univariate analysis		
Before PSM	3.602 (1.635-7.936)	0.001
After PSM	2.275 (1.022-5.067)	0.044
Multivariate analysis		
Before PSM	2.662 (1.173-6.043)	0.019
After PSM	2.641 (1.125-6.202)	0.026
Adjust the propensity score	2.861 (1.208-6.775)	0.017
IPTW	2.458 (1.159-5.213)	0.019

PSM, propensity score matching.

hyperglycemia in T2DM patients, which provides a conducive environment for the rapid growth and proliferation of cancer cells. In addition, high blood sugar will increase the expression of insulin and IGF-1, thereby indirectly promoting the proliferation of cancer cells. In vitro studies have shown that hyperglycemia increases the expression of advanced glycosylated end products, promotes the binding of advanced glycosylated end products to receptors, and then mediates the ERK/SP1/MMP2 pathway, leading to the migration of CRC cells [19]. The receptors of advanced glycosylation end products are related to inflammation, such as increasing the expression of interleukin-6, which can promote the occurrence of CRC [20].

Obesity is a common risk factor for both diabetes and CRC. Insulin resistance induced by obesity not only plays a growth-promoting role in CRC but also causes abnormal blood sugar in these patients and eventually develops T2DM. In addition, Postoperative CRC patients often receive glucocorticoids and targeted drugs to prevent recurrence, which can impair islet beta-cell function and decrease insulin sensitivity, thereby exacerbating insulin resistance [17]. Furthermore, tumor differentiation and TNM stage are recognized as important indices of the prognosis of tumor, reflecting the biological behavior of the tumor and the response of patients to treatment [21]. A lower differentiation degree means an increase in biological variability and malignancy of tumor cells, while a higher TNM stage indicates deeper invasion and more likely distant metastasis [22]. Finally, postoperative infection can produce various cytokines, maintaining a stable yet complex internal environment characterized by elements like tumor-infiltrating lymphocytes, tumor-associated macrophages, C-reactive protein, tumor necrosis factor-α, and interleukin-6. These inflammatory substances can enhance the kappa light chain pathway, signal transduction and transcriptional activator of B cells activated by nuclear factors 3 pathways, which promote the occurrence of CRC. Inflammation can also aggravate insulin resistance and hyperglycemia in T2DM patients, which together form an environment conducive to the survival of cancer cells [23, 24].

In a word, the interaction of these factors determines the long-term survival of patients with CRC, underscoring the importance of considering both the biological characteristics of the tumor and the overall health and complication management of the patients. To improve the therapeutic effect of CRC patients with T2DM, future work should be done with emphasis on optimizing preoperative blood glucose management, reducing surgical complications, and meeting the specific needs of different patients through personalized treatment programs. Although this is a retrospective study, the identified correlation provides a basis for future prospective research and clinical intervention. Future research should explore the interaction mechanism between T2DM and CRC, and the specific impact of blood glucose control on postoperative recovery and long-term survival, to develop more accurate treatment and management strategies.

To better predict the prognosis of CRC patients, we included the risk factors of the 5-year OS of CRC patients into the prediction model for the drawing and construction of a column graph, presented as a nomogram. Through internal verification, the model has demonstrated good degree of differentiation. The variables included in this study were all clinically available, making this prediction tool both practical and convenient for routine use. It provides a good basis for clinicians to evaluate the prognostic risk of CRC and make clinical decisions and provides specific indicators for reducing the

Table 4. Univariate Cox regression analysis of factors affecting 5-year survival in CRC patients

Variable	β	SE	Wald	P	HR	95% CI	
						Lower	Upper
Blood glucose situation	1.074	0.227	22.333	<0.001	2.928	1.875	4.573
Age	-0.222	0.417	0.283	0.595	0.801	0.354	1.813
Sex	-0.494	0.468	1.111	0.292	0.610	0.244	1.528
Body mass index	1.492	0.401	13.877	<0.001	4.446	2.028	9.747
History of hypertension	0.028	0.500	0.003	0.956	1.028	0.386	2.739
Tumor location	0.189	0.400	0.222	0.638	1.208	0.551	2.646
Histological type	0.154	0.546	0.080	0.777	1.167	0.401	3.400
Maximum tumor diameter	0.174	0.408	0.181	0.671	1.190	0.534	2.648
Differentiation Degree	2.465	0.431	32.767	<0.001	11.763	5.058	27.355
TNM stage	1.690	0.500	11.417	0.001	5.418	2.033	14.437
Surgical style	-0.068	0.403	0.029	0.886	0.934	0.424	2.058
Intraoperative blood loss	1.329	0.400	11.015	0.001	3.778	1.723	8.282
Postoperative chemotherapy	0.793	0.417	3.623	0.057	2.210	0.977	5.002
Postoperative infection	2.137	0.401	28.458	<0.001	8.478	3.866	18.592
Hospital stay	1.827	0.468	15.215	<0.001	6.216	2.482	15.569

TNM, tumor, node, metastasis; CRC, colorectal cancer.

Table 5. Variable assignment

Variable	Assignment condition
Blood glucose situation	1 = normal blood glucose levels; 2 = good blood glucose control; 3 = poor blood glucose control
Body mass index	1 = <25 kg/m^2; 2 = ≥25 kg/m^2
Differentiation degree	1 = medium + high differentiation; 2 = low differentiation
TNM stage	1 = I + II; 2 = III + IV
Intraoperative blood loss	1 = <300 ml; 2 = ≥300 ml
Postoperative infection	1 = no; 2 = yes
Hospital stay	1 = <30 d; 2 = ≥30 d

TNM, tumor, node, metastasis; CRC, colorectal cancer.

Table 6. Multivariate Cox regression analysis of factors affecting 5-year survival in CRC patients

Factor	β	SE	Wald	P	HR	95% CI	
						Lower	Upper
Blood glucose situation	0.803	0.244	10.871	0.001	2.233	1.385	3.599
Body mass index	0.910	0.433	4.410	0.036	2.484	1.063	5.808
Differentiation Degree	1.215	0.523	5.390	0.020	3.370	1.208	9.399
TNM stage	1.111	0.529	4.413	0.036	3.038	1.077	8.565
Intraoperative blood loss	0.679	0.443	2.354	0.125	1.973	0.828	4.700
Postoperative infection	0.982	0.486	4.086	0.043	2.671	1.030	6.924
Hospital stay	0.775	0.543	2.035	0.154	2.171	0.748	6.301

CRC, colorectal cancer.

occurrence of 5-year mortality of CRC. However, there are some limitations in our study. First of all, this is a retrospective study in a single center with small sample, which leads to bias in the selection of patients. Secondly, while the predictive model includes numerous relevant fac-

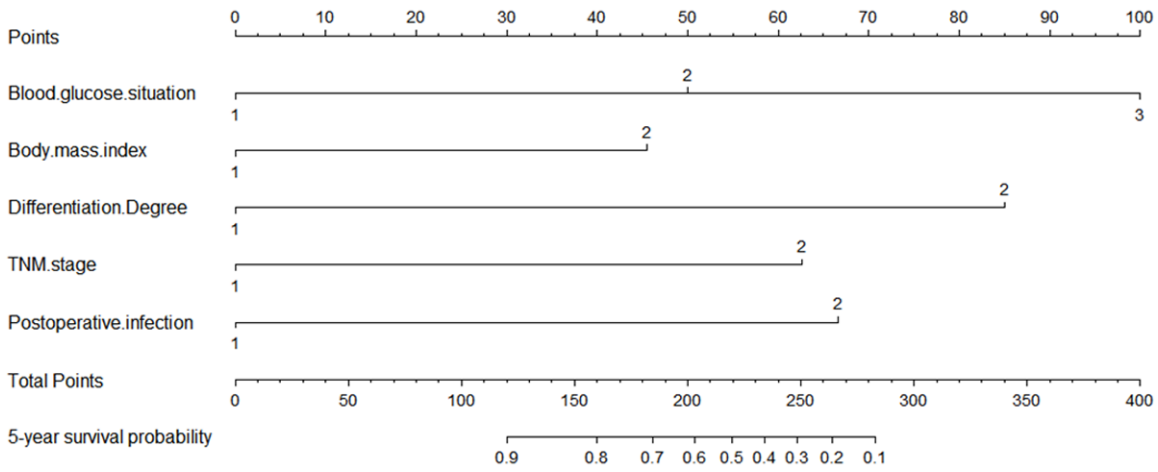

Figure 4. A nomogram predicting 5-year overall survival for colorectal cancer patients.

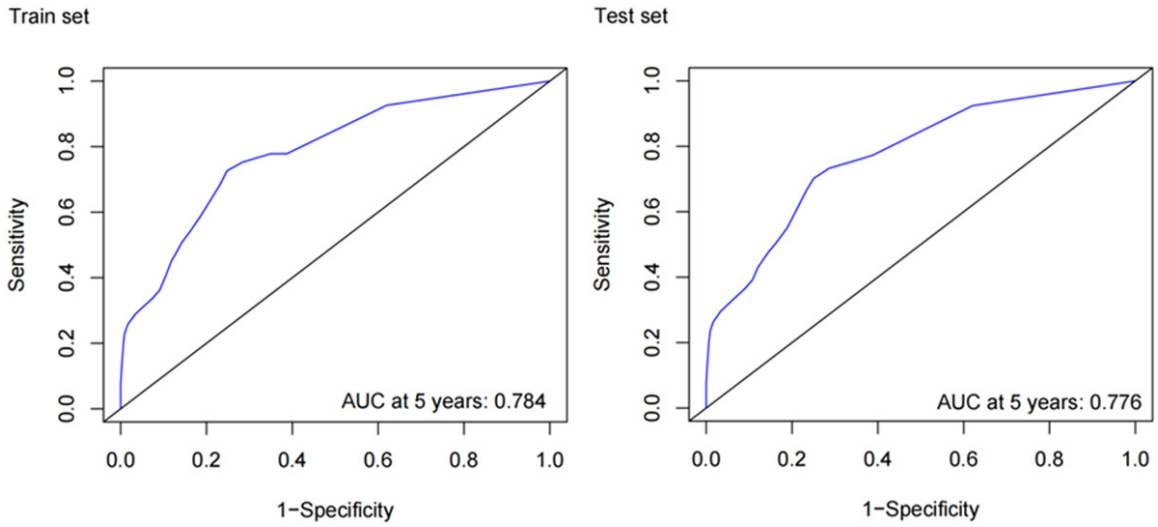

Figure 5. ROC curve of a nomogram predicting 5-year overall survival for colorectal cancer patients. ROC, receiver operating characteristics.

tors, it is impractical to account for all possible influencers in any prognostic model, and as such, some factors may have been omitted. In addition, the model lacks external validation. Therefore, high-quality multi-center and large-sample clinical studies are needed in the future, to obtain more accurate values and improve the accuracy of clinical decision-making.

Disclosure of conflict of interest

None.

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