



Effect of low-level creatinine clearance on short-term postoperative complications in patients with colorectal cancer

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Background: Renal function is closely related to cancer prognosis. Since preoperative renal insufficiency has been identified as a risk factor for postoperative complications, this study aimed to investigate the effect of preoperative creatinine clearance rate (CrCl) on short-term prognosis of patients undergoing colorectal surgery.

Methods: A retrospective analysis was conducted of the electronic health records of 526 adult patients who underwent elective colorectal cancer (CRC) surgery from September 2014 to February 2019 at the First Affiliated Hospital of Wenzhou Medical University. Cases were divided into two groups according to CrCl level and clinical variables were compared. Risk factors associated with postoperative complications were evaluated through univariate and multivariate logistic regression analyses.

Results: A total of 526 patients met the inclusion criteria. The overall rate of postoperative complications was 28.14%. Overall, the incidence of postoperative complications was significantly higher in the low CrCl patients. A low-level CrCl, multi-organ combined resection, and Charlson comorbidity index (CCI) were independent risk factors for short-term complications in patients with CRC. However, a low CrCl was identified as an independent risk factor for short-term postoperative complications in elderly, but not young patients in a subgroup analysis.

Conclusions: Preoperative low-level CrCl, multi-organ combined resection, and CCI were significant risk factors of postoperative complications in CRC patients. Preoperative low-level CrCl and multi-organ combined resection has a poor prognostic impact for elderly patients with CRC. These findings should have important implications for health care decision-making among patients with CRC who are at higher risk for post-operative complications.

Keywords: Outcomes; malignant tumor; renal function; hospitalization cost

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Introduction

Background

Colorectal cancer (CRC) is a common malignancy, with a prevalence putting it as the third most often occurring cancer and the second leading cause of mortality for cancer, accounting for 10.0% and 9.4% of cases, respectively (1). Additionally, it ranks within the top five tumors of mortality and incidence rates in China, indicating a persistent pattern of expansion (2). Surgical resection continues to be a primary therapeutic approach for CRC (3,4); nevertheless, the incidence of postoperative complications poses a significant challenge. Research findings have indicated that the incidence of postoperative complications in CRC ranges from 18% to 38% (5). Thus, it is necessary to analyze the risk factors for postoperative complications among CRC patients.

The phenomenon of aging population in China will result in a growing number of older individuals requiring medical care. The majority of older individuals exhibit a range of comorbidities, including pulmonary or cardiovascular conditions, which have been linked to unfavorable outcomes (6,7). On the contrary, the prognosis for older cancer patients is frequently determined by their physical state (8). Therefore, more attention should be paid to postoperative complications in elderly patients, particularly as they influence preoperative treatment and decision-making.

Preoperative renal insufficiency is significantly

associated with postoperative complications and may be underestimated (9). The estimation of glomerular filtration rate (GFR) can serve as an effective method for assessing preoperative renal function. Inulin renal clearance is the recognized gold standard for GFR determination (10), but inulin is expensive, the test requires continuous intravenous infusion of inulin, and the indwelling catheter, which is cumbersome to perform and determine. Estimated glomerular filtration rate (eGFR) is currently used as a common indicator to assess kidney function. However, despite being calculated using multiple formulas, each formula has its limitations in different populations. Creatinine clearance rate (CrCl) is another renal function indicator that can reduce the impact of body weight and age on prognosis. It provides a rough estimate of the number of functioning renal units and serves as a quantitative measure of kidney damage. Therefore, this prompts the consideration of serum CrCl as a viable alternative. This approach is popular owing to its expediency and simplicity, in contrast to the laborious process (11). Chronic renal insufficiency before surgery increases the risk of postoperative complications, according to research on adults with gastric cancer (12). We hypothesized that postoperative complications would be more common in CRC patients who had preoperative renal insufficiency. We thus sought to investigate the impact of CrCl on the short-term complication of CRC patients following surgery. Therefore, we aimed to characterize the association of preoperative levels of CrCl on the short-term postoperative complications of patients with CRC. We propose measures to minimize the risk of postoperative complications among this growing patient population. We present this article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-811/rc>).

Methods

Patients

From September 2014 to February 2019, we recruited 543 CRC patients at the Gastrointestinal Surgical Department at the First Affiliated Hospital of Wenzhou Medical University. The patients included in the study met the following criteria: (I) definitive diagnosis of CRC; (II) need for CRC surgical resection without receiving neoadjuvant chemotherapy or radiotherapy; (III) measurements of blood and biochemical indicators performed preoperatively and

Highlight box

Key findings

- Preoperative low-level creatinine clearance rate (CrCl) and multi-organ combined resection has a poor prognostic impact for colorectal cancer (CRC) elderly patients.

What is known and what is new?

- Multi-organ combined resection and Charlson comorbidity index are risk factors of postoperative complications in CRC patients.
- Preoperative low-level CrCl was identified as another significant risk factor of postoperative complications in CRC patients.

What is the implication, and what should change now?

- It is necessary to check, adjust, and stabilize the patient's renal function preoperatively and provide more comprehensive postoperative monitoring for patients requiring combined resection to reduce the occurrence and development of postoperative complications, especially for elderly patients aged >60 years.

within 7 days postoperatively; (IV) no relevant renal surgery in the preceding 3 weeks. A total of 17 patients were later excluded because of the following criteria: (I) preoperative chemotherapy or radiotherapy; (II) palliative surgery; (III) emergency surgery. Finally, a total of 526 patients were included in the analysis. All the operations were performed by chief surgeons, each of whom had worked on over 50 CRC cases. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The retrospective study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (2015-No.023) and individual consent for this retrospective analysis was waived.

Data sources

Pre-operative variables collected included patient clinicopathological characteristics such as age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, preoperative nutritional risk score [assessed within 24 h after admission using Nutritional Risk Screening (NRS) 2002 (13)], preoperative plasma albumin concentration (hypoalbuminemia defined as plasma albumin concentration <30 g/L), hemoglobin concentration (anemia defined as hemoglobin concentration <120 g/L for males and <110 g/L for females), neutrophil-to-lymphocyte ratio (NLR), preoperative comorbidity [calculated using Charlson comorbidity index (CCI) score], previous abdominal surgery history, smoking status, alcohol consumption status, disease stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) [tumor-node-metastasis (TNM)] classifications (14), preoperative biochemical indicators including serum calcium (hypocalcemia defined as serum calcium <2.25 mmol/L), serum potassium (hypokalemia defined as serum potassium <3.5 mmol/L), serum sodium (hyponatremia defined as serum sodium <135 mmol/L), serum chloride (hypochloremia defined as serum chloride <96 mmol/L), and serum creatinine. Variables collected of intra-operation details included tumor location (rectum or colon), operative type (although laparoscopic surgery was recommended to all patients, some chose open surgery because of previous abdominal surgery or could not consent to laparoscopic surgery for financial reasons), epidural anesthesia, combined resection, and operative time. Post-operative short-term outcomes were also collected, including complications within 30 days postoperatively, postoperative biochemical indicators (including serum calcium, serum potassium, serum sodium,

serum chlorine), length of stay, and hospitalization costs (cost analysis was conducted in Chinese Yuan).

According to the Clavien-Dindo classification (15), a postoperative complication was defined as a complication of grade II or higher which occurred within 30 days of surgery. The complications were classified into surgical complications and non-surgical complications. The complications were classified by two researchers according to the Clavien-Dindo classification.

Measurement of CrCl

CrCl can be obtained most accurately using 24-hour urine collection, but this method can be too laborious to be practical in routine clinical practice. Therefore, the Cockcroft-Gault (CG) equation (16), the most common equation in routine practice (17), was used to obtain CrCl in this study. Preoperatively, a serum sample containing blood and biochemical indicators was obtained from each patient. After we determined serum creatinine, we converted the units from mg/dL into $\mu\text{mol/L}$. Using the CG formula, we determined the CrCl.

According to the relevant literature, when the CrCl in adults falls below 80 mL/min, it indicates a decline in glomerular filtration function. If it decreases to 50–70 mL/min, it signifies mild impairment. Therefore, we use a CrCl <70 mL/min as a cutoff point to accurately identify the presence of renal dysfunction (18–20).

Statistical methods

The normal distribution of continuous data was determined using the Kolmogorov-Smirnov test. Normally distributed continuous data were shown as mean and standard deviation (SD), whereas non-normally distributed continuous data were shown as median and interquartile range. The categorical data were compared using the Pearson's χ^2 test or Fisher's exact test. In contrast, non-normally distributed continuous data and ranked data were examined using the Mann-Whitney *U* test. Meanwhile, the clinically relevant parameters were evaluated using univariate analysis to identify the potential outcome-associated risk factors. The variables with a *P* value <0.10 on univariate analysis were incorporated in the multivariate (logistic regression) analysis. *P* values <0.05 were considered statistically significant. SPSS 25.0 (IBM Corp., Armonk, NY, USA) was employed for all statistical analyses.

Results

Participants

We included 543 patients with CRC, 17 of whom were excluded due to the exclusion criteria. The final number of included patients was 526. The two groups were grouped according to CrCl level: and the number of patients in the two groups was 250 (CrCl <70 mL/min) and 276 (CrCl ≥70 mL/min), respectively.

Outcomes

Demographics of eligible patients are listed in *Table 1*. Overall, 420 of the 526 enrolled patients were above age 60 years. In total, 250 patients had a low CrCl. Meanwhile, 171 patients with a total score of 3 or higher in this study were identified as being at nutritional risk according to the NRS 2002.

As shown in *Table 1*, there was a significant intergroup difference in age, and a low CrCl was more likely to occur in patients above age 60 years ($P < 0.001$). At the same time, patients with a low CrCl had significantly higher NRS score and more comorbidities, along with lower BMI ($P < 0.001$), compared to those with a high CrCl. There is a correlation between NLR and CrCl, and patients with low CrCl have weaker immune function ($P = 0.012$). There was also a significant intergroup difference in terms of complications, and patients with a low CrCl had a higher incidence of complications ($P = 0.009$). There were no significant differences in surgery resection type, operation type, or type of anesthesia between the two groups.

Postoperative complications

We divided the postoperative complications into surgery-related complications and non-surgery-related complications (21) (*Table 2*). We found that patients with a low CrCl were more susceptible to surgery-related complications. The number and frequency of each complication are shown in *Table 3*. There were 195 postoperative events involving 148 patients (28.14%). Among the patients with complications, 84 (56.76%) had a low CrCl, including 115 postoperative events. Overall, the most frequent postoperative events were infection-related complications, including intra-abdominal infections, wound infection, and pulmonary infection.

Uni- and multi-variate analyses of variables associated with postoperative complications

Table 4 summarizes the related factors of complications after CRC surgery. Univariate analysis revealed that NRS ($P = 0.008$), CCI ($P = 0.013$), combined resection ($P = 0.015$), anemia ($P = 0.039$), and CrCl ($P = 0.009$) were associated with complications after CRC surgery. NRS, CCI, surgical method, combined resection, anemia, and CrCl were included in the multi-factor analysis because $P < 0.1$. Multivariate logistic regression analysis of these factors identified combined resection [odds ratio (OR) = 2.440; $P = 0.007$], CCI (OR = 1.321, $P = 0.014$), and CrCl (OR = 1.670, $P = 0.011$) as independently influential factors.

Uni- and multi-variate analyses of subgroups

We selected the age of 60 years to divide patients into old and young groups. This subgroup analysis revealed significant intergroup differences in the preoperative CrCl. In the old group (*Table 5*), NRS ($P = 0.012$), CrCl ($P = 0.009$), combined resection ($P = 0.034$), anemia ($P = 0.033$), CCI ($P = 0.012$), and surgery type ($P = 0.030$) were associated with postoperative complications. On multivariate logistic regression analysis, CrCl (OR = 1.842, $P = 0.008$), CCI (OR = 1.377, $P = 0.008$), and combined resection (OR = 2.408, $P = 0.025$) were independently associated factors of postoperative complications of CRC. However, in the young group (*Table 6*), we found that operating time (OR = 2.958, $P = 0.026$) was the only independent influential factor on both uni- and multi-variate analyses. We also found that elderly patients had significantly longer hospital stays than younger patients ($P < 0.001$) as well as higher hospitalization costs ($P < 0.001$).

Discussion

The current study showed that CrCl is an independent risk factor for short-term postoperative complications in patients with CRC. We also found that CrCl is an independent risk factor for short-term postoperative surgical-related complications in patients with CRC. A CrCl <70 mL/min indicates renal insufficiency (18,19). Therefore, preoperative renal insufficiency is accompanied by an increase in the incidence of short-term surgery-related complications in patients with CRC. Our conclusions are consistent with

Table 1 Patient demographic and clinical characteristics

Factors	Total (n=526) ^c	CrCl <70 mL/min (n=250) ^c	CrCl ≥70 mL/min (n=276) ^c	P value
Age				<0.001 ^d
≤60 y	106	12	94	
>60 y	420	238	182	
Gender				0.117
Male	313 (59.51)	147 (27.95)	166 (31.56)	
Female	213 (40.49)	103 (19.58)	110 (20.91)	
ASA grade				0.001 ^d
I	180 (34.22)	67 (12.74)	113 (21.48)	
II	279 (53.04)	141 (26.81)	138 (26.24)	
≥III	67 (12.74)	42 (7.98)	25 (4.75)	
NRS				<0.001 ^d
<3	355 (67.49)	142 (27.00)	213 (40.49)	
≥3	171 (32.51)	108 (20.53)	63 (11.98)	
BMI ^b , kg/m ²	22.76 (3.10)	21.66 (2.94)	23.76 (2.90)	<0.001 ^d
Operating time, min ^a	170.50 [77]	170.00 [78]	171.00 [83]	0.423
Prior abdominal surgery				0.870
Yes	112 (21.29)	54 (10.27)	58 (11.03)	
No	414 (78.71)	196 (37.26)	218 (41.44)	
CCI				0.001 ^d
0	277 (52.66)	116 (22.05)	161 (30.61)	
1	179 (34.03)	89 (16.92)	90 (17.11)	
≥2	70 (13.31)	45 (8.56)	25 (4.75)	
Tumor location				0.295
Rectum	242 (46.01)	121 (23.00)	121 (23.00)	
Colon	284 (53.99)	129 (24.52)	155 (29.47)	
Epidural anesthesia				0.094
Yes	301 (57.22)	153 (29.09)	148 (28.14)	
No	225 (42.78)	97 (18.44)	128 (24.33)	
Surgical method				0.109
Laparoscopic surgery	276 (52.47)	122 (23.19)	154 (29.28)	
Open surgery	250 (47.53)	128 (24.33)	122 (23.19)	
Combined resection				0.025 ^d
Yes	43 (8.17)	13 (2.47)	30 (5.70)	
No	483 (91.83)	237 (45.06)	246 (46.77)	

Table 1 (continued)

Table 1 (continued)

Factors	Total (n=526) ^c	CrCl <70 mL/min (n=250) ^c	CrCl ≥70 mL/min (n=276) ^c	P value
TNM stages				0.929
1–2	318 (60.46)	152 (28.90)	166 (31.56)	
3–4	208 (39.54)	98 (18.63)	110 (20.91)	
Smoking				0.833
Yes	99 (18.82)	48 (9.13)	51 (9.70)	
No	427 (81.18)	202 (38.40)	225 (42.78)	
Drinking				0.065
Yes	91 (17.30)	35 (6.65)	56 (10.65)	
No	435 (82.70)	215 (40.87)	220 (41.83)	
Neutrophil-to-lymphocyte ratio				0.012
≥3.02	171 (32.51)	95 (18.06)	76 (14.45)	
<3.02	355 (67.49)	155 (29.47)	200 (38.02)	
Postoperative complications				0.009 ^d
Yes	148 (28.14)	84 (15.97)	64 (12.17)	
No	378 (71.86)	166 (31.56)	212 (40.30)	
Hemoglobin, g/L ^a	120.00 [32]	119.00 [28]	122.00 [33]	0.133
Serum albumin, g/L ^a	37.80 (6.00)	36.9 (5.75)	38.4 (5.80)	0.461
Serum calcium, mmol/L ^b	2.20 (0.14)	2.18 (0.14)	2.22 (0.14)	0.002 ^d
Serum potassium, mmol/L ^a	3.9 (0.53)	3.91 (0.55)	3.88 (0.51)	0.485
Serum sodium, mmol/L ^a	140 [3]	140 [3]	139 [3]	0.484
Serum chlorine, mmol/L ^a	105 [4]	105 [4]	105 [3]	0.625

^a, values are median (interquartile range); ^b, values are mean (standard deviation); ^c, values are number of patients and percent unless indicated otherwise; ^d, statistically significant, P<0.05. CrCl, creatinine clearance; y, years; ASA, American Society of Anesthesiology; NRS, nutritional risk screening; BMI, body mass index; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis.

Table 2 Detailed information on postoperative complications

Classification	Total (n=526) ^a	CrCl <70 mL/min (n=250) ^a	CrCl ≥70 mL/min (n=276) ^a	P value
Total complications	148 (28.14)	84 (15.97)	64 (12.17)	0.009 ^b
Surgery-related complications	113 (21.48)	65 (12.36)	48 (9.13)	0.019 ^b
No surgery-related complications	35 (6.65)	19 (3.61)	16 (3.04)	0.484

^a, values are number of patients and percent; ^b, statistically significant. CrCl, creatinine clearance.

those of previous studies that have reported an increased risk of complications due to renal insufficiency in general and vascular (non-cardiac) surgery (22) and an associated increased risk of death and hospitalization as the result of increased disease burden (23). This may be due to the

relationship between kidney function and the immune system. Decreasing renal function affects the immune system. In the study, patients with CrCl <70 mL/min had lower immune capacity, which may lead to intestinal barrier dysfunction and increased systemic inflammation (24).

Table 3 Actual number and frequency of each complication

Infection-related complications	Total ^a	CrCl <70 mL/min ^a	CrCl ≥70 mL/min ^a
Intra-abdominal infection	37 (7.03)	24 (4.56)	13 (2.47)
Wound infection	33 (6.27)	16 (3.04)	17 (3.23)
Pulmonary infection	25 (4.75)	14 (2.66)	11 (2.09)
Venous thrombosis	25 (4.75)	17 (3.23)	8 (1.52)
Anastomotic leakage	20 (3.80)	12 (2.28)	8 (1.52)
Bowel obstruction	15 (2.85)	6 (1.14)	9 (1.71)
Gastrointestinal dysfunction ^c	8 (1.52)	4 (0.76)	4 (0.76)
Postoperative bleeding	6 (1.14)	2 (0.38)	4 (0.76)
Urinary system	6 (1.14)	5 (0.95)	1 (0.19)
Cardiac complications	2 (0.38)	2 (0.38)	0 (0.00)
Coagulopathy	1 (0.38)	0 (0.00)	1 (0.19)
Pulmonary embolism	2 (0.38)	1 (0.19)	1 (0.19)
Others ^b	15 (2.85)	12 (2.28)	3 (0.57)

Values in parentheses are percentages unless indicated otherwise. ^a, there were some patients who experienced more than one complication category. The total number of the complications was greater than that of the patients who experienced complications; ^b, others contain 4 severe complications (death, autonomic disorder, pulmonary embolism, renal insufficiency) and 2 mild complications (abdominal and pleural effusion); ^c, including postoperative vomiting, diarrhea, gastroparesis, and abdominal distension. CrCl, creatinine clearance.

Concurrently, existing literature shows that a systemic inflammatory response causes a poor prognosis in patients with CRC (25-27).

Patients with renal insufficiency who undergo surgery impose a direct financial burden on society and their families (28-30). This study explored the relationship between preoperative CrCl levels and short-term postoperative complications in CRC surgery. To ensure good renal function, more stringent fluid management and nephrotoxicity avoidance for patients expecting CRC surgery must be implemented. Therefore, hetastarch should be avoided because of its severe adverse effects (31). In contrast, a concentrated albumin solution (20–25%) is a good choice that can provide some benefits (32).

In this study, we found that age had a significant effect on CrCl (33-35), so we grouped patients by age and performed a subgroup analysis. Between the two groups, there was a significant difference in the effect of low CrCl on postoperative complications. In the elderly group, patients with a low CrCl were more likely to have postoperative complications, whereas there was no significant effect in the young group. This phenomenon may have a certain

relationship with age itself since the decrease in CrCl with age represents true renal aging (34,36) and renal function decreases with age (37,38). Another possible reason is that elderly patients often have impaired nutritional status, especially those admitted to the hospital (39). However, young patients have better physical compensatory abilities because their compensated kidney function is still normal, thus reducing the preoperative prognosis value.

In China, the direct treatment of CRC may sometimes be catastrophic for CRC patients (40). In our study, we found that older patients had significantly longer hospital stays and more expensive hospitalization costs than younger adults. Thus, a poor prognosis can increase the economic burden on society and families. Therefore, more attention should be paid to the adjustment of the preoperative condition of elderly patients and to the maintenance of stable kidney function preoperatively (41-43). For young people, this requirement may not be very strict, but it is still necessary to maintain good renal function.

In this study, some of our patients underwent multi-organ combined resection, including the liver, gallbladder, and spleen. Related studies have shown that the incidence

Table 4 Univariate and multivariate logistic regression analysis of factors associated with postoperative complications

Factors	Total (n=526)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=148)	Non-postoperative complications (n=378)	P value	OR (95% CI)	P value
Age				0.718		
>60 y	420	120	300			
≤60 y	106	28	78			
Gender				0.989		
Male	313	88	225			
Female	213	60	153			
ASA grade				0.108		
I	180	46	134			
II	279	77	202			
≥III	67	25	42			
NRS				0.008 ^a		
<3	355	87	268			
≥3	171	61	110			
BMI, kg/m ²				0.818		
<18.5	45	14	31			
18.5–24	303	84	219			
>24	178	50	129			
Operating time				0.425		
>210 min	133	41	92			
≤210 min	393	107	286			
Prior abdominal surgery				0.725		
Yes	112	33	79			
No	414	115	299			
CCI				0.013 ^a	1.321 (1.058–1.650)	0.014 ^a
0	277	68	209			
1	179	52	127			
≥2	70	28	42			
Tumor location				0.571		
Rectum	242	71	171			
Colon	284	77	207			
Epidural anesthesia				0.892		
Yes	301	84	217			
No	225	64	161			
Surgical method				0.065		
Laparoscopic surgery	276	68	208			
Open surgery	250	80	170			

Table 4 (continued)

Table 4 (continued)

Factors	Total (n=526)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=148)	Non-postoperative complications (n=378)	P value	OR (95% CI)	P value
Combined resection				0.015 ^a	2.440 (1.269–4.692)	0.007 ^a
Yes	43	19	24			
No	483	129	354			
TNM stages				0.428		
1–2	318	94	224			
3–4	208	54	154			
Smoking				0.202		
Yes	99	33	66			
No	427	115	312			
Drinking				0.721		
Yes	91	27	64			
No	435	121	314			
Hypoalbuminemia				0.180		
Yes	31	12	19			
No	495	136	359			
Anemia				0.039 ^a		
Yes	167	57	110			
No	359	91	268			
Hypocalcemia				0.385		
Yes	261	78	183			
No	265	70	195			
Hypokalemia				>0.99		
Yes	68	19	49			
No	458	129	329			
Hyponatremia				>0.99		
Yes	19	5	14			
No	507	143	364			
Hypochloremia				>0.99		
Yes	4	1	3			
No	522	147	375			
CrCl				0.009 ^a	1.670 (1.123–2.482)	0.011 ^a
<70 mL/min	250	84	166			
≥70 mL/min	276	64	212			

^a, statistically significant (P<0.05). OR, odds ratio; CI, confidence interval; y, years; ASA, American Society of Anesthesiology; NRS, nutritional risk screening, BMI, body mass index; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis; CrCl, creatinine clearance.

Table 5 Univariate and multivariate logistic regression analysis of factors associated with postoperative complications of elderly patients

Factors	Total (n=420)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=120)	Non-postoperative complications (n=300)	P value	OR (95% CI)	P value
Gender				0.590		
Male	257	71	186			
Female	163	49	114			
ASA grade				0.063		
I	113	27	86			
II	243	69	174			
≥III	64	24	40			
NRS				0.012 ^a		
<3	260	63	197			
≥3	160	57	103			
BMI, kg/m ²				0.939		
<18.5	38	12	26			
18.5–24	244	67	177			
>24	138	41	97			
Operating time				0.902		
>210 min	108	30	78			
≤210 min	312	90	222			
Prior abdominal surgery				0.795		
Yes	92	25	67			
No	328	95	233			
CCI				0.012 ^a	1.377 (1.087–1.744)	0.008 ^a
0	195	46	149			
1	156	47	109			
≥2	69	27	42			
Tumor location				0.478		
Rectum	202	61	141			
Colon	218	59	159			
Epidural anesthesia				0.635		
Yes	256	71	185			
No	164	49	115			
Surgical method				0.030 ^a		
Laparoscopic surgery	201	47	154			
Open surgery	219	73	146			

Table 5 (continued)

Table 5 (continued)

Factors	Total (n=420)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=120)	Non-postoperative complications (n=300)	P value	OR (95% CI)	P value
Combined resection				0.034 ^a	2.408 (1.118–5.189)	0.025 ^a
Yes	31	14	17			
No	389	106	283			
TNM stages				0.440		
1–2	257	77	180			
3–4	163	43	120			
Smoking				0.502		
Yes	79	25	54			
No	341	95	246			
Drinking				0.885		
Yes	69	19	50			
No	351	101	250			
Hypoalbuminemia				0.078		
Yes	25	11	14			
No	395	109	286			
Anemia				0.033 ^a		
Yes	139	49	90			
No	281	71	210			
Hypocalcemia				0.130		
Yes	219	70	149			
No	201	50	151			
Hypokalemia				>0.99		
Yes	54	15	39			
No	366	105	261			
Hyponatremia				>0.99		
Yes	15	4	11			
No	405	116	289			
Hypochloremia				0.501		
Yes	2	1	1			
No	418	119	299			
CrCl				0.009 ^a	1.842 (1.171–2.897)	0.008 ^a
<70 mL/min	238	80	158			
≥70 mL/min	182	40	142			

^a, statistically significant (P<0.05). OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiology; NRS, nutritional risk screening, BMI, body mass index; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis; CrCl, creatinine clearance.

Table 6 Univariate and multivariate logistic regression analysis of factors associated with postoperative complications of young patients

Factors	Total (n=106)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=28)	Non-postoperative complications (n=78)	P value	OR (95% CI)	P value
Gender				0.382		
Male	50	17	39			
Female	56	11	39			
ASA grade				0.659		
I	67	19	48			
II	36	8	28			
≥III	3	1	2			
NRS				0.429		
<3	95	24	71			
≥3	11	4	7			
BMI, kg/m ²				0.522		
<18.5	7	2	5			
18.5–24	59	17	42			
>24	40	9	31			
Operating time				0.023 ^a	2.958 (1.140–7.677)	0.026 ^a
>210 min	25	11	14			
≤210 min	81	17	64			
Prior abdominal surgery				0.126		
Yes	20	8	12			
No	86	20	66			
CCI				0.846		
0	82	22	60			
1	23	5	18			
≥2	1	1	0			
Tumor location				0.825		
Rectum	40	10	30			
Colon	66	18	48			
Epidural anesthesia				0.620		
Yes	45	13	32			
No	61	15	46			
Surgical method				0.635		
Laparoscopic surgery	75	21	54			
Open surgery	31	7	24			

Table 6 (continued)

Table 6 (continued)

Factors	Total (n=106)	Univariate analysis			Multivariate analysis	
		Postoperative complications (n=28)	Non-postoperative complications (n=78)	P value	OR (95% CI)	P value
Combined resection				0.203		
Yes	12	5	7			
No	94	23	71			
TNM stages				0.824		
1–2	61	17	44			
3–4	45	11	34			
Smoking				0.126		
Yes	20	8	12			
No	86	20	66			
Drinking				0.234		
Yes	22	8	14			
No	84	20	64			
Hypoalbuminemia				>0.99		
Yes	6	1	5			
No	100	27	73			
Anemia				0.790		
Yes	28	8	20			
No	77	20	57			
Hypocalcemia				0.184		
Yes	42	8	34			
No	64	20	44			
Hypokalemia				0.844		
Yes	14	4	10			
No	92	24	68			
Hyponatremia				>0.99		
Yes	4	1	3			
No	102	27	75			
Hypochloremia				>0.99		
Yes	2	0	2			
No	104	28	76			
CrCl				0.564		
<70 mL/min	12	4	8			
≥70 mL/min	94	24	70			

^a, statistically significant (P<0.05). OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiology; NRS, nutritional risk screening; BMI, body mass index; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis; CrCl, creatinine clearance.

of postoperative complications is higher in cases of multiple organ resection (44-46). This finding is consistent with our study, in which multi-organ combined resection was a significant independent risk factor for short-term complications after CRC. The reason for this may be related to greater tissue damage and larger incisions resulting from multi-organ combined resection surgery. However, combined resection can reduce the burden on the heart and lungs associated with multiple anesthesia exposures and can reduce hospitalization costs (47). Therefore, for patients who require multiple organ resection, we recommend the surgery be performed by an experienced team and adequate intensive care be provided to reduce postoperative risk, especially for elderly patients.

Elderly patients with CRC often have multiple comorbidities. We can use the most extensive CCI system, and CCI can be applied to most malignant tumors (48). In this study, CCI was an important predictor of short-term postoperative complications in patients with CRC. Elderly patients with greater CCI may have a higher incidence of postoperative complications. Therefore, for these patients, we need to consider surgery for CRC after treating the comorbidities.

This present study had several limitations. First, we used the CG formula for creatinine measurements instead of urine CrCl. This may have led to a degree of deviation between the CrCl used in the CG formula and the actual CrCl of the same patient. Second, large-scale, multi-center studies are needed to analyze whether this relationship exists in other regions since this was a single-center study with a relatively small sample size. Third, for the age category analysis, we used a cutoff at 60 years, and an analysis of other age categories is required in the future. Fourth, like all retrospective studies, ours could have possible errors in data collection and was susceptible to selection bias.

Conclusions

This study explored the relationship between preoperative CrCl levels and short-term postoperative complications in CRC surgery. A low CrCl, multi-organ combined resection, and CCI were independent risk factors for short-term complications. For the elderly, the incidence of postoperative complications was significantly increased with low CrCl and multi-organ resection. Therefore, we must optimize the patient's renal function preoperatively and provide more intensive postoperative monitoring for elderly

CRC surgery patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (2015-No.023) and individual consent for this retrospective analysis was waived.

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References

- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49.
- Qiu H, Cao S, Xu R. Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. *Cancer Commun (Lond)* 2021;41:1037-48.
- Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014;383:1490-502.
- Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. *Lancet* 2019;394:1467-80.
- Nowakowski M, Pisarska M, Rubinkiewicz M, et al. Postoperative complications are associated with worse survival after laparoscopic surgery for non-metastatic colorectal cancer - interim analysis of 3-year overall survival. *Wideochir Inne Tech Maloinwazyjne* 2018;13:326-32.
- Boakye D, Rillmann B, Walter V, et al. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: A systematic review and meta-analysis. *Cancer Treat Rev* 2018;64:30-9.
- Artiles-Armas M, Roque-Castellano C, Fariña-Castro R, et al. Impact of frailty on 5-year survival in patients older than 70 years undergoing colorectal surgery for cancer. *World J Surg Oncol* 2021;19:106.
- Landi F, Vallribera F, Rivera JP, et al. Morbidity after laparoscopic and open rectal cancer surgery: a comparative analysis of morbidity in octogenarians and younger patients. *Colorectal Dis* 2016;18:459-67.
- Blitz JD, Shoham MH, Fang Y, et al. Preoperative Renal Insufficiency: Underreporting and Association With Readmission and Major Postoperative Morbidity in an Academic Medical Center. *Anesth Analg* 2016;123:1500-15.
- Zhang Y, Sui Z, Yu Z, et al. Accuracy of iohexol plasma clearance for GFR-determination: a comparison between single and dual sampling. *BMC Nephrol* 2018;19:174.
- Dooley MJ, Singh S, Rischin D. Rounding of low serum creatinine levels and consequent impact on accuracy of bedside estimates of renal function in cancer patients. *Br J Cancer* 2004;90:991-5.
- Cheng YX, Tao W, Liu XY, et al. Does Chronic Kidney Disease Affect the Surgical Outcome and Prognosis of Patients with Gastric Cancer? A Meta-Analysis. *Nutr Cancer* 2022;74:2059-66.
- Kondrup J, Rasmussen HH, Hamberg O, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003;22:321-36.
- Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;67:93-9.
- Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187-96.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
- Stevens LA, Coresh J, Greene T, et al. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473-83.
- NADIG PW, VALK WL. The serum creatinine and endogenous creatinine clearance as tests of renal function. *J Urol* 1961;86:157-62.
- Terasawa H, Kinugasa H, Ako S, et al. Utility of liquid biopsy using urine in patients with pancreatic ductal adenocarcinoma. *Cancer Biol Ther* 2019;20:1348-53.
- Ge J, Jin Z, Feng X, et al. Creatinine clearance rate predicts prognosis of patients with systemic lupus erythematosus: a large retrospective cohort study. *Clin Rheumatol* 2021;40:2221-31.
- ten Broek RP, Strik C, Issa Y, et al. Adhesiolysis-related morbidity in abdominal surgery. *Ann Surg* 2013;258:98-106.
- Gaber AO, Moore LW, Aloia TA, et al. Cross-sectional and case-control analyses of the association of kidney function staging with adverse postoperative outcomes in general and vascular surgery. *Ann Surg* 2013;258:169-77.
- Liao YC, Chang CC, Chen CY, et al. Preoperative renal insufficiency predicts postoperative adverse outcomes in a mixed surgical population: a retrospective matched cohort study using the NSQIP database. *Int J Surg* 2023;109:752-9.
- Yang T, Richards EM, Pepine CJ, et al. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. *Nat Rev Nephrol* 2018;14:442-56.
- Suzuki Y, Okabayashi K, Hasegawa H, et al. Comparison of Preoperative Inflammation-based Prognostic Scores in Patients With Colorectal Cancer. *Ann Surg* 2018;267:527-31.
- Hanus M, Parada-Venegas D, Landskron G, et al. Immune System, Microbiota, and Microbial Metabolites: The

- Unresolved Triad in Colorectal Cancer Microenvironment. *Front Immunol* 2021;12:612826.
27. Wang H, Tian T, Zhang J. Tumor-Associated Macrophages (TAMs) in Colorectal Cancer (CRC): From Mechanism to Therapy and Prognosis. *Int J Mol Sci* 2021;22:8470.
 28. Collins AJ, Foley RN, Chavers B, et al. United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis* 2012;59:A7-e420.
 29. Liu ZH. Nephrology in china. *Nat Rev Nephrol* 2013;9:523-8.
 30. Hengstmann JH, Dengler HJ, Geipert F. Proceedings: The conversion of cyclamate to cyclohexylamine in 255 diabetic and obese patients. *Naunyn Schmiedebergs Arch Pharmacol* 1974;282:suppl 282:R31.
 31. Srivastava A. Fluid Resuscitation: Principles of Therapy and "Kidney Safe" Considerations. *Adv Chronic Kidney Dis* 2017;24:205-12.
 32. Mårtensson J, Bellomo R. Does fluid management affect the occurrence of acute kidney injury? *Curr Opin Anaesthesiol* 2017;30:84-91.
 33. Hayashi T, Aoyama T, Tanabe K, et al. Low creatinine clearance is a risk factor for D2 gastrectomy after neoadjuvant chemotherapy. *Ann Surg Oncol* 2014;21:3015-22.
 34. Hommos MS, Glasscock RJ, Rule AD. Structural and Functional Changes in Human Kidneys with Healthy Aging. *J Am Soc Nephrol* 2017;28:2838-44.
 35. Chang-Panesso M. Acute kidney injury and aging. *Pediatr Nephrol* 2021;36:2997-3006.
 36. Rowe JW, Andres R, Tobin JD, et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol* 1976;31:155-63.
 37. Jassal SK, von Muhlen D, Barrett-Connor E. Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. *J Bone Miner Res* 2007;22:203-10.
 38. O'Sullivan ED, Hughes J, Ferenbach DA. Renal Aging: Causes and Consequences. *J Am Soc Nephrol* 2017;28:407-20.
 39. John BK, Bullock M, Brenner L, et al. Nutrition in the elderly. Frequently asked questions. *Am J Gastroenterol* 2013;108:1252-66; quiz 1267.
 40. Huang HY, Shi JF, Guo LW, et al. Expenditure and financial burden for the diagnosis and treatment of colorectal cancer in China: a hospital-based, multicenter, cross-sectional survey. *Chin J Cancer* 2017;36:41.
 41. Lee MS, Tanaka K. Significance of health fitness appraisal in an aging society. *Appl Human Sci* 1997;16:123-31.
 42. Ushida K, Yamamoto Y, Hori S, et al. The effect of preoperative rehabilitation on the prevention of postoperative ileus in colorectal cancer patients. *Support Care Cancer* 2023;31:123.
 43. Audisio RA. Preoperative evaluation of the older patient with cancer. *J Geriatr Oncol* 2016;7:409-12.
 44. Bartoş A, Bartoş D, Dunca F, et al. Multi-organ resections for colorectal cancer: analysis of potential factors with role in the occurrence of postoperative complications and deaths. *Chirurgia (Bucur)* 2012;107:476-82.
 45. Huang ZX, Zhou Z, Shi HR, et al. Postoperative complications after robotic resection of colorectal cancer: An analysis based on 5-year experience at a large-scale center. *World J Gastrointest Surg* 2021;13:1660-72.
 46. Wasmann KATGM, Klaver CEL, van der Bilt JDW, et al. Subclassification of Multivisceral Resections for T4b Colon Cancer with Relevance for Postoperative Complications and Oncological Risks. *J Gastrointest Surg* 2020;24:2113-20.
 47. Kim HJ, Choi GS, Park JS, et al. Simultaneous laparoscopic multi-organ resection combined with colorectal cancer: comparison with non-combined surgery. *World J Gastroenterol* 2012;18:806-13.
 48. Huang Y, Zhang Y, Li J, et al. Charlson comorbidity index for evaluation of the outcomes of elderly patients undergoing laparoscopic surgery for colon cancer. *J BUON* 2017;22:686-91.

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