



# Serum C-Reactive Protein-to-Body Mass Index Ratio Predicts Overall Survival in Patients With Resected Colorectal Cancer

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## Abstract

**Background and Purpose:** Systemic inflammation and nutritional status have been shown to be associated with the prognosis of colorectal cancer. The purpose of this study was to evaluate the impact of the serum C-reactive protein-to-body mass index ratio on the prognosis of patients with curatively resected colorectal cancer. **Methods:** We conducted a retrospective analysis of a database of 2,471 eligible patients with colorectal cancer who underwent curative resection at our hospital between 2004 and 2019. The optimal cut-off for CPR-to-BMI ratio was determined using maximally selected rank statistics. Patients were divided into 2 groups according to the cut-off value of the serum C-reactive protein-to-body mass index ratio. Kaplan-Meier curves and Cox regression analysis were used to compare overall survival. A two-sided  $P$ -value  $< 0.05$  was considered statistically significant. **Results:** The proportion of patients with a high C-reactive protein-to-body mass index ratio increased with increasing age, male sex, right-sided colon cancer, poorly differentiated tumors, advanced-stage disease, local/distant metastases, tumor–node–metastasis stage, and microsatellite instability. In subgroup analysis according to tumor–node–metastasis stage, the overall survival of the high C-reactive protein-to-body mass index ratio group was significantly shorter than that of the low C-reactive protein-to-body mass index ratio group ( $P < 0.001$ ). Multivariate analysis identified age, differentiation, tumor–node–metastasis stage, carcinoembryonic antigen level, and the C-reactive protein-to-body mass index ratio as independent poor prognostic factors for overall survival. **Conclusions:** The C-reactive protein-to-body mass index ratio predicts the prognosis of patients with curatively resected colorectal cancer and is an independent risk factor for overall survival in patients with colorectal cancer.

## Keywords

body mass index, colorectal neoplasms, C-reactive protein, prognosis, survival

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## Introduction

In recent years, colorectal cancer (CRC) has become the third most common malignancy worldwide, and is a leading cause of cancer-related deaths.<sup>1</sup> In the United States alone, it is estimated that there were 145,600 new cases of CRC and 51,020 deaths in 2019.<sup>2</sup> Therefore, it is important to identify risk factors that may be used to screen high-risk patients and treat them more aggressively to improve their prognosis.

An increasing number of studies<sup>3,4</sup> have shown that systemic inflammation is associated with the prognosis of CRC. Some researchers have begun to study the relationship between inflammatory biomarkers and CRC. Encouragingly, they found

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that several inflammatory biomarkers and their derivatives, such as C-reactive protein (CRP),<sup>5</sup> lymphocyte-to-monocyte ratio,<sup>6</sup> neutrophil-to-lymphocyte ratio,<sup>6,7</sup> and platelet-to-lymphocyte ratio, can predict the prognosis of patients with CRC.<sup>8</sup> Other researchers have shown that nutritional status can also affect the prognosis of patients with CRC.<sup>9</sup> The prognostic nutritional index is a value that is calculated from several indicators (including serum albumin concentration). It represents the general nutritional status of patients and is a standard marker of nutritional status (like albumin). Recently, the prognostic nutritional index has been reported to be associated with the prognosis of CRC.<sup>10,11</sup> Serum albumin levels have been shown to be an independent prognostic factor in patients with CRC, and patients with low serum albumin levels have a poor prognosis.<sup>12,13</sup>

The Glasgow Prognostic Score and modified Glasgow Prognostic Score are novel inflammatory-nutritional indices that use CRP and albumin concentrations. Meta-analyses have shown that they are effective prognostic indicators for OS in patients with CRC.<sup>14,15</sup> It is noteworthy that these prognostic markers take into consideration both inflammation and nutrition. However, research is lacking on the effects of inflammation and nutritional status on the prognosis of patients with CRC. Therefore, the aim of this study was to evaluate the prognostic value of the CRP-to-body mass index (BMI) (CRP-to-BMI) ratio in patients with CRC.

## Materials and Methods

### Ethics Approval and Informed Consent

The study design was approved by the Ethics and Human Subject Committee of Guangxi Medical University Cancer Hospital (approval No. LW2021037). Informed consent was obtained from all participants.

### Patients and Eligibility Criteria

We conducted a retrospective analysis of a database of 2,471 patients with CRC who underwent curative resection at Guangxi Medical University Cancer Hospital between 2004 and 2019. The inclusion criteria were patients with histologically confirmed CRC who underwent resection of the primary tumor and received no treatment prior to the blood test. The exclusion criteria included a history of familial adenomatous polyposis or hereditary non-polyposis colon cancer, fever at the time of blood collection, or other concurrent malignancies.

### Preoperative Assessment of Patient Data

Patient demographics and preoperative clinicopathological characteristics, including age, sex, tumor location, differentiation, tumor–node–metastasis (TNM) stage, T stage, N stage, M stage, *KRAS* phenotype, microsatellite instability

status, BMI, CRP level, and carcinoembryonic antigen (CEA) level, were obtained. Tumor pathological staging was performed according to the Union for International Cancer Control TNM classification system (8th edition).<sup>16</sup> Venous blood samples were collected on the second morning after fasting for  $\geq 8$  hours after admission. Blood tests were performed within 2 weeks before surgery. Body weight and height measurements were also taken within 2 weeks before surgery. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Curative resection was defined as the absence of any gross residual tumor from the surgical bed and a surgical resection margin that was pathologically negative for tumor invasion.

### Follow-Up and Survival

Follow-up was conducted by telephone and outpatient consultation in accordance with the National Comprehensive Cancer Network guidelines. Overall survival (OS) was defined as the interval (in months) between the date of surgery and the date of death or last follow-up (December 2019).

### Statistical Analysis

In order to obtain the optimal cut-off values of the CRP-to-BMI ratio, we used the maximum selection rank statistic to determine the potential cut-off point in the predicted value of the OS ratio variable. For each potential cut-off point, calculate the absolute value of the standardized log-rank statistics. When the standardized statistics reach the maximum value, the cut-off point where the survival outcome are best divided into 2 groups is selected as the optimal cut-off point. Based on this optimal cut-off point, we divided the data into 2 groups: high CRP-to-BMI ratio group and low CRP-to-BMI ratio group. Chi-square tests (categorical variables) and Student's *t*-tests (continuous variables) were used to analyze the relationships between clinicopathological characteristics and the CRP-to-BMI ratio. OS was estimated using the Kaplan-Meier method and compared by the log-rank test. Univariate, multivariate, and subgroup survival analyses were performed using Cox regression models. Hazard ratios and 95% confidence intervals were calculated.

All statistical analyses were conducted using R software (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria). Univariate and multivariate analyses were performed using the “survival” package in R (version 3.1-8). A two-sided *P*-value of  $< 0.05$  was considered statistically significant.

## Results

### Baseline Patient Characteristics

Based on the inclusion and exclusion criteria, 2,471 patients with CRC who underwent curative resection at our hospital between 2004 and 2019 were enrolled. Patients were divided into 2 groups according to the cut-off value of the CRP-to-BMI

ratio, which was set at 0.27. Patients with a CRP-to-BMI ratio of  $>0.27$  were included in the high CRP-to-BMI ratio group. Conversely, patients with a CRP-to-BMI ratio of  $<0.27$  were included in the low CRP-to-BMI ratio group. Significant differences in age, sex, tumor location, differentiation, TNM stage, T stage, M stage, microsatellite instability status, BMI, CRP level, and CEA level were observed between the high and low CRP-to-BMI ratio groups (all  $P < 0.05$ ). The proportion of patients with a high CRP-to-BMI ratio increased with increasing age, male sex, right-sided colon cancer, poorly differentiated tumors, advanced-stage disease, local/distant metastases, TNM stage, and microsatellite instability. Compared with those in the low CRP-to-BMI ratio group, patients in the high CRP-to-BMI ratio group had a lower BMI, higher CEA level, and higher CRP level. Conversely, there were no significant differences in N stage or *KRAS* phenotype between the high and low CRP-to-BMI ratio groups (both  $P > 0.05$ ; Table 1). This relationship is shown more intuitively in Figure 1.

#### Kaplan-Meier Curves According to TNM Stage

Kaplan-Meier survival curves were used to analyze the relationship between the CRP-to-BMI ratio and prognosis according to TNM stage. OS was significantly shorter in the high CRP-to-BMI ratio group than in the low CRP-to-BMI ratio group (all TNM stages,  $P < 0.001$ ; Figure 2A). For patients with stage I/II ( $P = 0.02$ ) or III/IV CRC ( $P < 0.001$ ), OS was significantly longer in the low CRP-to-BMI ratio group than in the high CRP-to-BMI ratio group (Figure 2B-C). This suggests that the CRP-to-BMI ratio can predict the prognosis of patients with CRC according to TNM stage, with a low CRP-to-BMI ratio associated with a more favorable outcome.

#### Kaplan-Meier Curves According to CRP-to-BMI Ratio Combined With Other Clinicopathological Characteristics

The effect of the CRP-to-BMI ratio on OS combined with other clinicopathological characteristics was also analyzed using Kaplan-Meier survival curves. The results showed that in the same age group, a high CRP-to-BMI ratio was often associated with a poorer prognosis (Figure 3A). OS was significantly shorter in the high CRP-to-BMI ratio group than in the low CRP-to-BMI ratio group, regardless of tumor location (left vs. right; Figure 3B). In the *KRAS* wild-type and mutant groups, a high CRP-to-BMI ratio tended to be associated with a poorer prognosis (Figure 3C). In the high CRP-to-BMI ratio group, patients with microsatellite-stable CRC had a poorer prognosis than those with microsatellite-unstable CRC (Figure 3D). Female sex was also associated with a poorer prognosis in the high CRP-to-BMI ratio group (Figure 3E). These findings suggest that the prognosis of patients with CRC can still be determined after combining the CRP-to-BMI ratio with clinicopathological

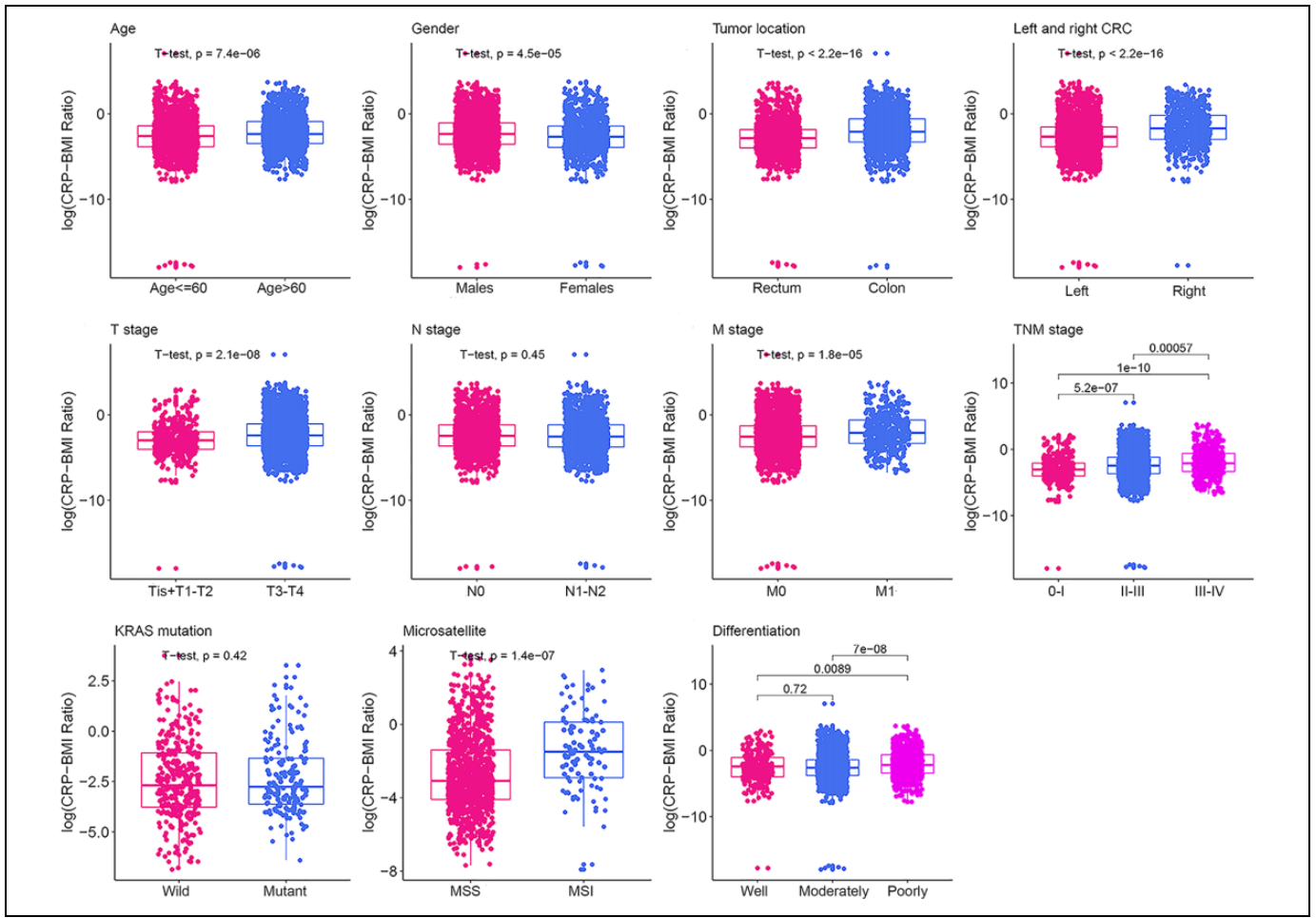
**Table 1.** Baseline Characteristics According to the CRP-to-BMI Ratio.

Features	Case	CBR		P
		Low ( $\leq 0.27$ )	High ( $> 0.27$ )	
Total	2471	1593	878	
Gender (%)				$< 0.001$
Male	1500 (60.7)	925 (58.1)	575 (65.5)	
Female	971 (39.3)	668 (41.9)	303 (34.5)	
Location (%)				$< 0.001$
Left-sided	1888 (76.4)	1311 (82.3)	577 (65.7)	
Right-sided	583 (23.6)	282 (17.7)	301 (34.3)	
Differentiation (%)				$< 0.001$
Well	222 (9.0)	140 (8.8)	82 (9.3)	
Moderately	1576 (63.8)	1077 (67.6)	499 (56.8)	
Poorly	673 (27.2)	376 (23.6)	297 (33.8)	
pT-stage (%)				$< 0.001$
Tis+T1-2	401 (16.2)	304 (19.1)	97 (11.0)	
T3-4	2070 (83.8)	1289 (80.9)	781 (89.0)	
pN-stage (%)				0.70
N0	1362 (55.1)	874 (54.9)	488 (55.6)	
N1-2	1109 (44.9)	719 (45.1)	390 (44.4)	
pM-stage (%)				$< 0.001$
M0	2095 (84.8)	1385 (86.9)	710 (80.9)	
M1	376 (15.2)	208 (13.1)	168 (19.1)	
pTNM stage (%)				$< 0.001$
0	23 (0.9)	15 (0.9)	8 (0.9)	
I	287 (11.6)	225 (14.1)	62 (7.1)	
II	938 (38.0)	574 (36.0)	364 (41.5)	
III	847 (34.3)	571 (35.8)	276 (31.4)	
IV	376 (15.2)	208 (13.1)	168 (19.1)	
KRAS mutation (%)				0.70
Wild	323 (13.1)	205 (12.9)	118 (13.4)	
Mutant	171 (6.9)	114 (7.2)	57 (6.5)	
NA	1977 (80.0)	1274 (80.0)	703 (80.1)	
Microsatellite status (%)				$< 0.001$
MSS	1000 (40.5)	699 (43.9)	301 (34.3)	
MSI	101 (4.1)	42 (2.6)	59 (6.7)	
NA	1370 (55.4)	852 (53.5)	518 (59.0)	
Age (Year, mean (SD))	2471	57.29 (12.62)	59.12 (13.31)	0.001
BMI (kg/m <sup>2</sup> , mean (SD))	2471	22.32 (3.08)	21.54 (3.16)	$< 0.001$
CRP (mg/L, mean (SD))	2471	2.53 (1.65)	29.41 (36.02)	$< 0.001$
CEA (ng/ml, mean (SD))	2471	15.58 (59.76)	33.12 (111.16)	$< 0.001$

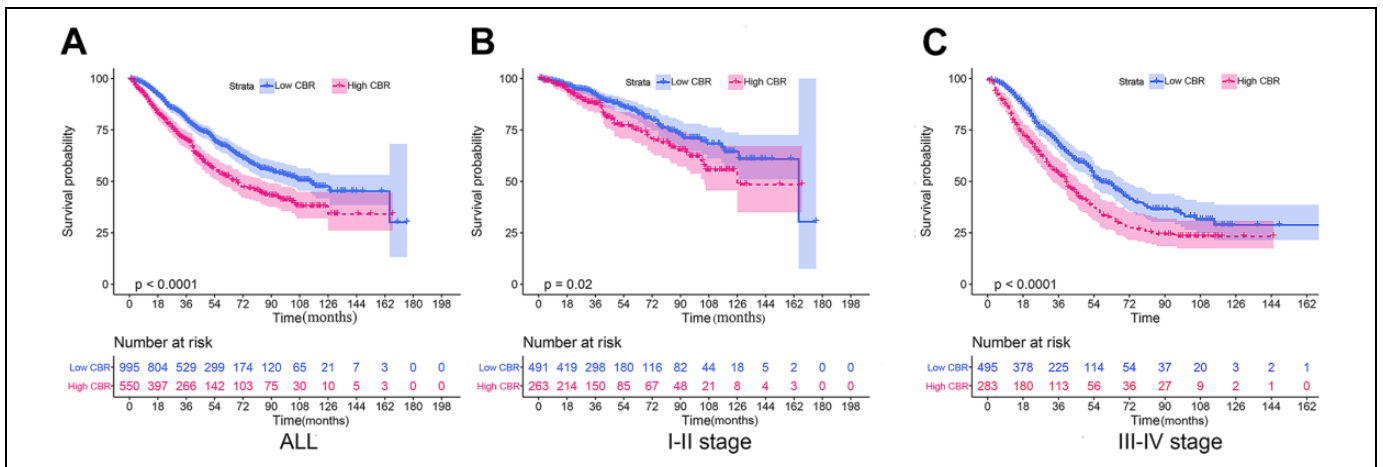
characteristics. The prognosis of the low CRP-to-BMI ratio group was more favorable than that of the high CRP-to-BMI ratio group.

#### Univariate, Multivariate, and Subgroup Analyses

In the univariate analysis, age ( $P = 0.019$ ), tumor location (left vs. right;  $P = 0.022$ ), differentiation ( $P < 0.001$ ), TNM stage ( $P < 0.001$ ), CEA level ( $P < 0.001$ ), CRP level ( $P < 0.001$ ), and the CRP-to-BMI ratio ( $P < 0.001$ ) were



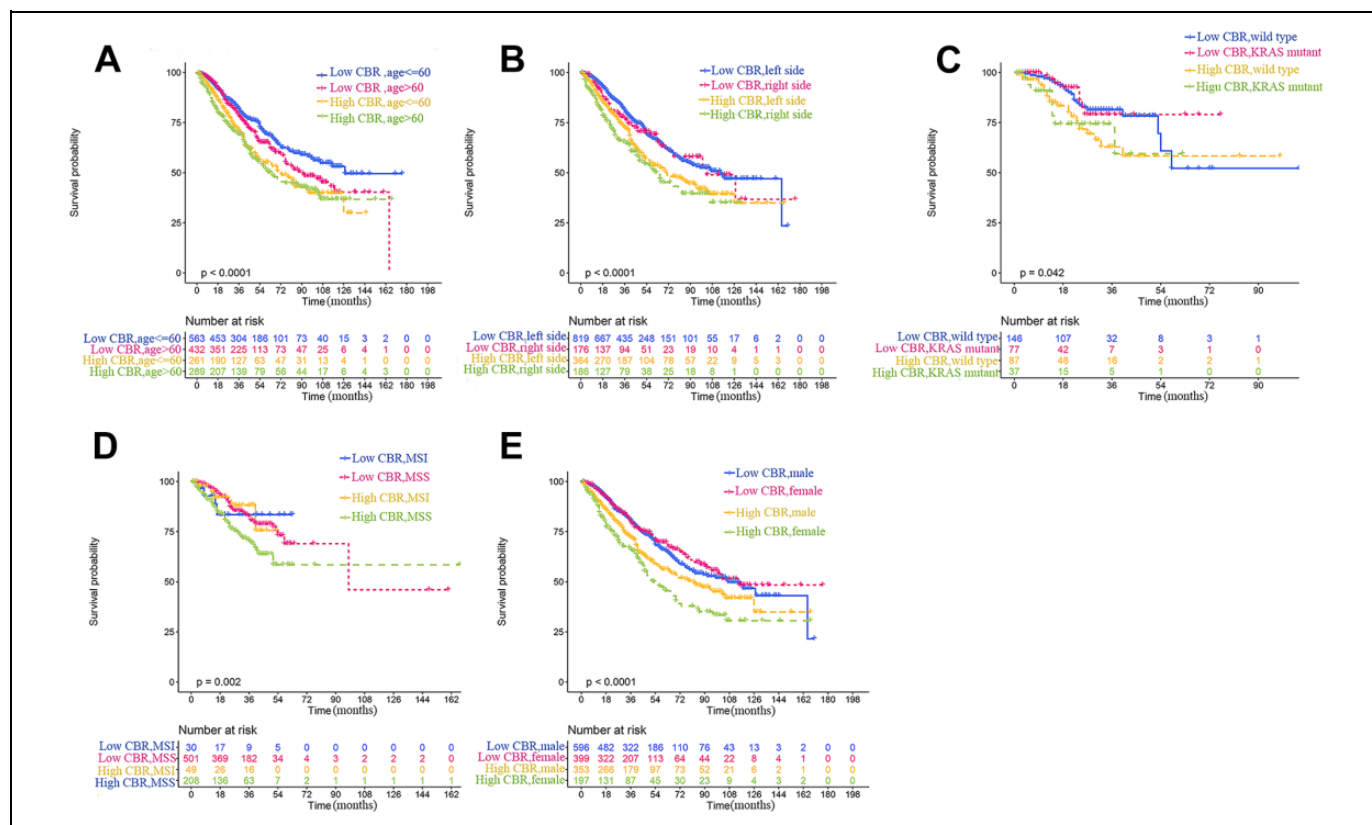
**Figure 1.** Box plots showing the relationships between the CRP-to-BMI ratio and clinicopathological characteristics. BMI indicates body mass index; CRP, C-reactive protein.



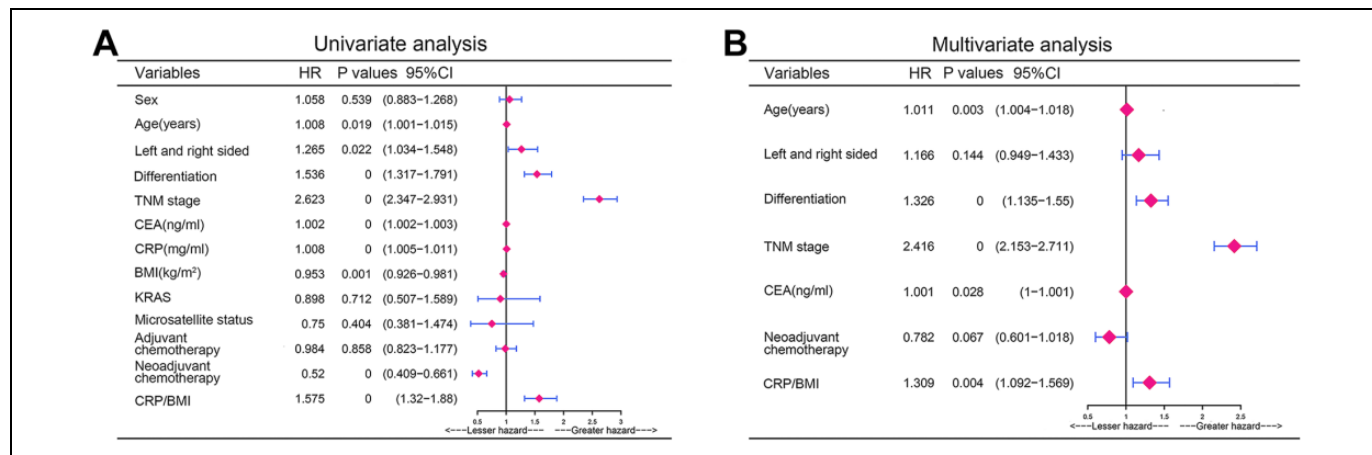
**Figure 2.** OS stratified by the CRP-to-BMI ratio according to tumor stage. Kaplan-Meier curves of OS in (A) all stages of CRC, (B) stage I/II CRC, and (C) stage III/IV CRC. The optimal cut-off value of the CRP-to-BMI ratio was 0.27. BMI indicates body mass index; CRC, colorectal cancer; CRP, C-reactive protein; OS, overall survival.

identified as risk factors for CRC. Neoadjuvant chemotherapy ( $P < 0.001$ ) and BMI ( $P = 0.001$ ) were considered protective factors (Figure 4A). However, in the multivariate analysis, only

TNM stage ( $P < 0.001$ ), differentiation ( $P < 0.001$ ), and the CRP-to-BMI ratio ( $P = 0.004$ ) were confirmed as independent risk factors for OS in patients with CRC (Figure 4B).



**Figure 3.** OS according to the CRP-to-BMI ratio combined with other clinicopathological characteristics. Kaplan-Meier curves of OS: the CRP-to-BMI ratio combined with (A) age, (B) tumor location, (C) *KRAS* phenotype, (D) microsatellite instability status, and (E) sex. The optimal cut-off value of the CRP-to-BMI ratio was 0.27. BMI indicates body mass index; CRP, C-reactive protein; OS, overall survival.

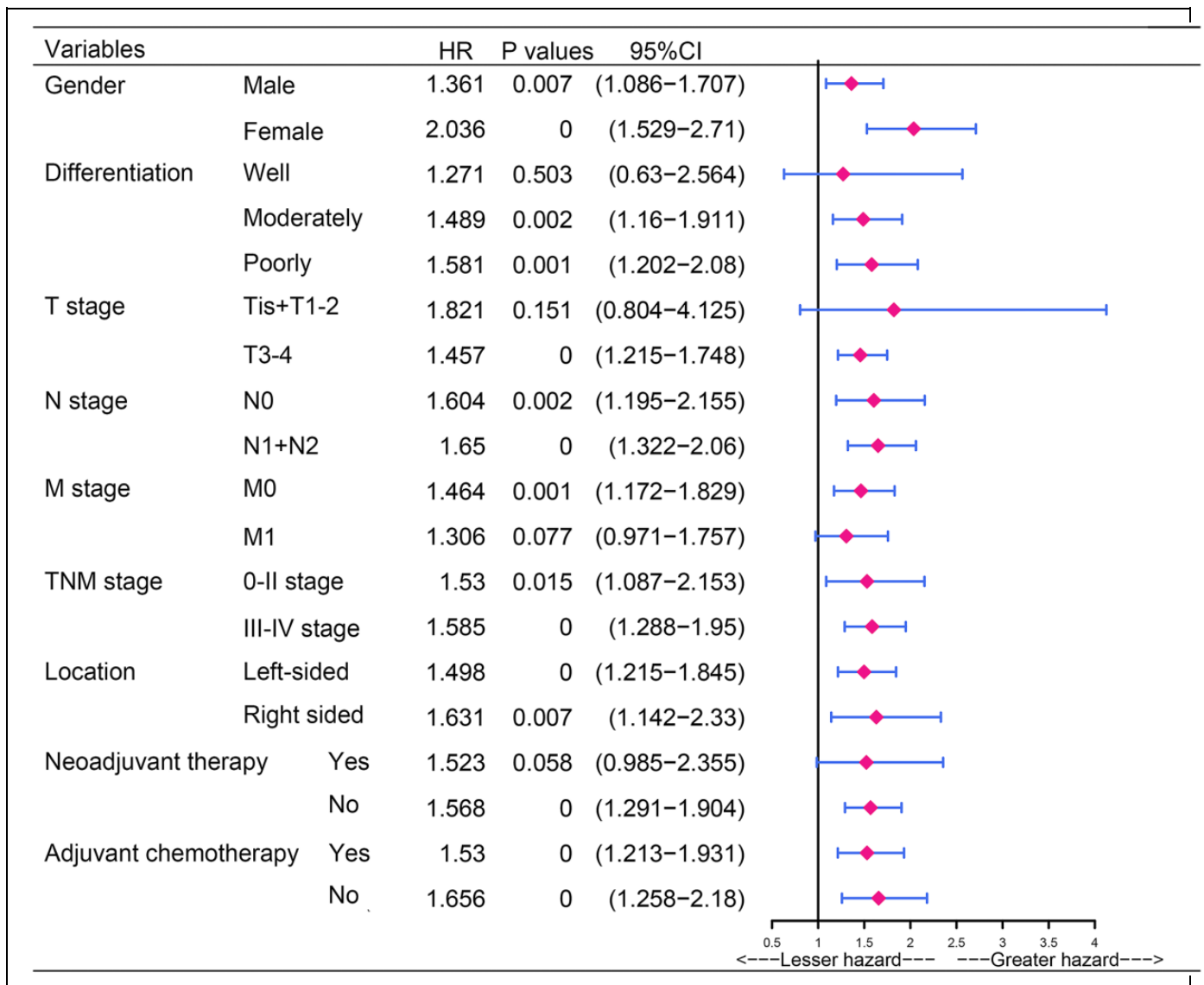


**Figure 4.** Cox regression analysis of OS in patients with CRC. (A) Univariate and (B) multivariate analysis of clinicopathological characteristics. CRC indicates colorectal cancer; OS, overall survival.

To investigate the prognostic value of the CRP-to-BMI ratio in patients with different clinicopathological characteristics, we performed a subgroup analysis (Figure 5). Univariate analysis revealed that female sex, poor differentiation, advanced N stage, the absence of distant metastases, advanced TNM stage, and non-chemotherapy combined with a high CRP-to-BMI ratio was associated with a poor prognosis.

### Discussion

The major strength of this study is that it presents a novel inflammatory-nutritional index, the CRP-to-BMI ratio, that strongly predicts poor prognosis in patients with CRC. To the best of our knowledge, this is one of the few large-scale retrospective studies to take into consideration both inflammatory biomarkers and nutritional indicators.



**Figure 5.** Subgroup analysis of patients stratified according to different clinicopathological characteristics.

In this study, an optimal CRP-to-BMI ratio cut-off value of 0.27 was obtained through the relationship between the CRP-to-BMI ratio and OS. We demonstrated that the CRP-to-BMI ratio can predict the prognosis of patients with CRC. First, we stratified patients into high and low CRP-to-BMI ratio groups using the optimal cut-off value for the CRP-to-BMI ratio. Significant differences in age, sex, tumor location, differentiation, TNM stage, T stage, M stage, microsatellite instability status, BMI, and CRP level were observed between the 2 groups. Kaplan-Meier survival curves were used to compare OS between the high and low CRP-to-BMI ratio groups according to TNM stage and different clinicopathological characteristics. The results showed that the high CRP-to-BMI ratio group had a poorer prognosis. Finally, univariate and multivariate analyses identified the CRP-to-BMI ratio as an independent predictor of poor prognosis in patients with CRC. These findings suggest that the CRP-to-BMI ratio is a

predictor of the prognosis of CRC that may be used in addition to TNM stage.

Accumulating evidence suggests that systemic inflammation not only promotes the development of malignant tumors, but also plays an important role in the survival of patients with cancer.<sup>17</sup> There is no doubt that systemic inflammation is also associated with CRC.<sup>3</sup> CRP is an acute-phase protein that is synthesized by the liver during inflammation and is a reliable marker of systemic inflammation.<sup>18,19</sup> It is commonly used to assess the extent of systemic inflammation. It has also been used to predict the prognosis of patients with various inflammation-related diseases.<sup>20</sup> Recent studies have shown that there is an association between elevated CRP levels and the risk of multiple cancers, including CRC, breast cancer, ovarian cancer, and urinary system cancer.<sup>21-24</sup> Therefore, CRP level is a prognostic indicator of CRC.<sup>25</sup> Similar results were also found in our study (hazard ratio: 1.008, 95% confidence



interval: 1.005-1.011). A plausible explanation is that the growth and invasion of colorectal tumors can lead to inflammation of the surrounding tissues, resulting in the production of interleukin-6 (IL-6). More importantly, CRC cells can secrete a series of cytokines, including IL-6.<sup>26</sup> IL-6 can regulate CRP expression at the transcriptional level in hepatocytes, and IL-6 levels positively correlate with serum CRP levels.<sup>19,27</sup> A high serum IL-6 concentration has been shown to be associated with a poor prognosis in patients with CRC.<sup>28,29</sup> Hence, a high pre-operative CRP level is one indicator of a poor prognosis in patients with CRC.

BMI is often used as an objective marker to assess patients' nutritional status. Individuals with a high BMI (>25 kg/m<sup>2</sup>) have a higher incidence of cancer. However, patients with a high BMI at initial diagnosis have a better prognosis than those with a low BMI.<sup>30</sup> In this study, we found that the median BMI was significantly higher in the low CRP-to-BMI ratio group than in the high CRP-to-BMI ratio group ( $P < 0.001$ ). In the univariate analysis, BMI was identified as a protective factor for CRC. This indirectly shows that patients with a high BMI have a better prognosis, meaning BMI is a good prognostic factor for CRC. However, it is unclear what level of BMI can achieve a better prognosis. This was beyond the scope of the present study.

The current prognostic factors and treatment options for patients with CRC are diverse. However, TNM stage, extent of tumor differentiation, and postoperative pathology remain the main influencing factors. Performed postoperatively, it is difficult to predict survival and decide on further treatment before surgery. In this study, the CRP-to-BMI ratio combined CRP level and BMI. It not only reflects the relationship between systemic inflammation and nutritional status, but also serves as an independent predictor of OS in patients with CRC. It can predict the prognosis of patients with CRC better than either CRP level or BMI alone, close to the extent of tumor differentiation, and second to TNM stage. Furthermore, the composition parameters of the CRP-to-BMI ratio are readily available and inexpensive, and can be measured in any hospital. Therefore, it can better predict OS and optimize treatment strategies for patients with CRC before surgery.

This study has several limitations. First, this was a single-center retrospective study. Consequently, our findings will require further validation. Second, the data collected only included patients who had undergone curative resection. Therefore, the data do not represent patients with unresectable tumors or those who refused surgical intervention for various reasons. Third, we lack the analysis of disease-free survival, therefore, we cannot predict the duration of the patient's tumor-free state. Finally, the patients were enrolled between 2004 and 2019. During these 15 years, advances in surgical technology and the development of detection equipment may have had an impact on the results.

## Conclusion

In conclusion, the CRP-to-BMI ratio predicts the prognosis of patients with curatively resected CRC and is an independent

risk factor for OS in patients with CRC. It may help to identify high-risk patients and optimize preoperative treatment decisions.

## Authors' Note

Lingxu Huang, MD, Jungang Liu, PhD, and Xiaoliang Huang, MD, contributed equally to this work. Conception and design: LH, JL, XH, HL, and WT. Acquisition of data: LH, JL, XH, CW, XM, HZ, DL, LZ and HL. Analysis or interpretation of data: LH, JL, YM, and XH. Contributed analysis tools: LH, JL, XH, CW, HL, and WT. Drafted the manuscript and revised it critically for important intellectual content: LH, XH, CW, XM, YM, HZ and WT. All authors have approved the final version and agree to be 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 design was approved by the Ethics and Human Subject Committee of Guangxi Medical University Cancer Hospital (approval No. LW2021037). Informed consent was obtained from all participants.


## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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