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Original Research Article

Cumulative C-reactive Protein in the Perioperative Period as a Novel Marker for Oncological Outcome in Patients with Colorectal Cancer Undergoing Curative Resection

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Abstract

Objectives: Systemic inflammatory response is strongly associated with poor oncological outcome in colorectal cancer (CRC). Perioperative inflammation caused by surgical stress can lead to the development of postoperative infectious complications (PIC) as well as cancer-related inflammation. We aimed to evaluate the prognostic potential of perioperative systemic inflammation by calculating the time-dependent cumulative C-reactive protein (CRP) levels during the perioperative period.

Methods: We analyzed clinicopathological data from 540 patients with CRC who underwent potentially curative surgery at our institution. The time-dependent aggregated CRP level was denoted "cumulative CRP," which represents the area under the line of time (days) and the CRP levels preoperatively and on postoperative days 1, 3, and 7.

Results: Cumulative CRP was significantly higher in patients with CRC undergoing open surgery than in patients undergoing laparoscopic surgery. In multivariate analysis, high cumulative CRP was an independent prognostic factor for disease-free survival (DFS) and overall survival (OS) in both the laparoscopic and open surgery groups. Patients with CRC and high cumulative CRP had significantly poorer DFS and OS than those with low cumulative CRP, including those patients without PIC.

Conclusions: Cumulative CRP is an independent predictive marker of OS and DFS in patients with CRC who undergo curative surgery.

Keywords

cumulative C-reactive protein, colorectal cancer, prognosis

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide[1]. Despite the development of radical surgery and multimodal therapies such as chemotherapy and chemoradiotherapy, the disease recurs in approximately 15%-30% of patients[2,3]. A major prognostic indicator for oncological outcome is the TNM classification, which is defined according to pathologic features[4]. Tumor-host interactions are mediated by a complex network of cytokines, chemokines, growth factors, and matrix remodeling enzymes that reach beyond the local tumor microenvironment and evoke systemic responses[5-7]. Recently, cancer-associated inflammation has been linked to the pathogenesis of many adult malignancies and is now recognized as the seventh "hallmark" of cancer[5]. Systemic inflammation is

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most common in patients with poorly differentiated and advanced stage CRC; inflammation is also an independent factor of less favorable outcome[8-11]. Several preoperative inflammatory indexes such as the modified Glasgow Prognostic Score (mGPS) using C-reactive protein (CRP) and albumin[11], neutrophil to lymphocyte ratio[12], CRP to albumin ratio[13], and albumin to globulin ratio[14] have been associated with poor oncological outcome. In addition, previous studies have demonstrated an association between early postoperative inflammation status using CRP and neutrophil to lymphocyte ratio and poor oncological outcome[15-17]. For example, CRP levels on postoperative day 4 or the maximum CRP levels during the period from surgical resection to discharge were related to worse survival[16,17]. Postoperative inflammation is induced by surgical trauma and dynamically changes from day to day with postoperative infectious complications (PIC), such as surgical site infection (SSI) and remote infection (RI) in patients with CRC[18-20]. Therefore, preoperative inflammatory status, surgical stress, and development of PIC should be accurately evaluated as cumulative overall perioperative inflammation for predicting oncological outcome. We aimed to evaluate the prognostic potential of perioperative systemic inflammation using time-dependent aggregation of CRP levels from the preoperative period to postoperative day 7 in patients with CRC who undergo curative surgery.

Methods

Patients

We enrolled 540 patients who underwent potentially curative surgery for CRC at our institution between January 1, 2005, and December 31, 2015. Curative resection was defined as the absence of gross residual tumor in the surgical bed and a resection margin that was pathologically negative for tumor invasion. The patients were classified according to the TNM Classification of Union for International Cancer Control, 8th Edition. The patients granted their informed consent and were followed according to our standard protocol every 12-16 weeks. The protocol included tumor marker studies, computed tomography, endoscopic examination, ultrasonography, and chest radiography. This study was approved by the institutional review board of the Mie University Hospital.

Clinical and laboratory data collection

Data collected from inpatient and outpatient records included age and sex, tumor location (rectum or colon), neoadjuvant chemoradiotherapy (CRT), surgical procedure (open surgery or laparoscopic surgery), pathological characteristics (tumor staging, lymph node metastasis, tumor-cell differentiation, and lymphovascular invasion), carcinoembryonic antigen (CEA) levels at diagnosis, onset of PIC such as SSI and RI, disease-free survival (DFS), and overall survival (OS). All patients who were converted from laparoscopic surgery to open surgery were included in the open surgery group. OS was defined as the time from the date of surgery to the day of death from any cause. DFS was defined as the time from the date of surgery to the day of the first recurrence or death from any cause. PIC was defined as all SSI and RI that occurred within one month after surgery. CRP levels were quantified before surgery and at postoperative day (POD) 1, POD3, and POD7. The accumulated CRP level was denoted "cumulative CRP" and obtained by summing the area of each trapezoid calculated from the CRP levels preoperatively and at POD1, POD3, and 7 and time (days) (Figure 1). The cut-off value for CEA was 5 ng/mL, according to the normal range used in our hospital. The cut-off values for cumulative CRP were calculated in the open surgery and laparoscopic surgery groups separately, according to the receiver operating characteristic (ROC) curves for DFS. The cut-off values were defined as 57.8 and 24.1 in the open surgery and laparoscopic surgery groups, respectively.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Comparisons were performed using the Mann-Whitney test. The optimal cut-off values of cumulative CRP were determined at the point on the ROC curve with the maximum Youden's index (sensitivity + specificity − 1) for survival. Survival curves were generated using the Kaplan-Meier product-limit method, and comparisons were performed using the log-rank test. Prognostic factors were identified using univariate and multivariate analyses (Cox proportional-hazards regression model). All P-values were two-sided, and $P < 0.05$ was considered significant. All statistical analyses were performed using JMP 11 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

This retrospective study included 321 male and 219 female patients with a median age of 68 years (range, 32-94 years). The number of patients undergoing laparoscopic and open surgery was 271 and 269, respectively. The median follow-up was 52.9 months (mean ± SD: 52.3 ± 33.8). Three (0.6%), 171 (31.7%), 187 (34.6%), and 179 (33.1%) patients had (y)pStage 0, I, II, and III CRC, respectively. In total, 116 patients were treated with preoperative chemoradiotherapy; among them, 106 (19.6%) had disease recurrence after surgery with curative intent. Patients undergoing open surgery had a more advanced stage and PIC compared

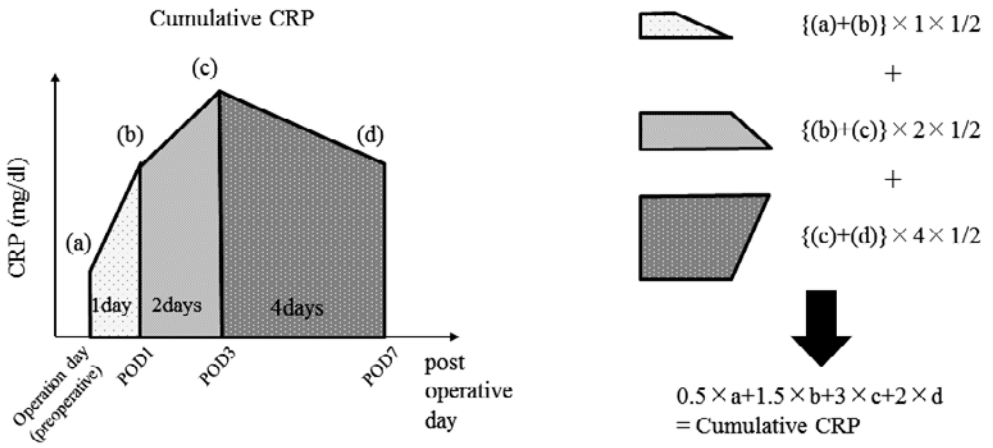

Figure 1. Definition of cumulative C-reactive protein (CRP). Cumulative CRP is defined as the aggregate of perioperative CRP levels (i.e., preoperative, postoperative day (POD) 1, POD3, and POD7). The aggregate is calculated as the sum of the area of each trapezoid (a, b, c, and d).

Table 1. Patient Characteristics According to Surgical Procedure.

Variables		Laparoscopic surgery n = 271	Open surgery n = 269	*P*-value
Age	<68	132	142	0.3431
	≥68	139	127	
Gender	female	121	98	0.0518
	male	150	171	
Serosal invasion	T1 + 2 + 3	258	218	**<0.0001**
	T4	13	51	
Lymph node metastasis	absent	194	166	**0.0149**
	present	77	103	
Histology	well/mod	263	234	0.2731
	por/muc	8	35	
Lymphatic invasion	absent	124	81	**0.0002**
	present	147	188	
Venous invasion	absent	166	138	**0.0197**
	present	105	131	
Location	colon	173	109	**<0.0001**
	rectum	98	160	
Chemoradiotherapy	no	261	163	**<0.0001**
	yes	10	106	
PIC	absent	234	195	**<0.0001**
	present	37	74	
CEA	≤5 ng/mL	178	104	**<0.0001**
	>5 ng/mL	89	134	

PIC, postinfectious complication; CEA carcinoembryonic antigen. Median age at surgery was 68 years in this cohort. Bold font indicates statistical significance.

with those undergoing laparoscopic surgery (Table 1).

Perioperative CRP levels and cumulative CRP in open and laparoscopic surgeries

The mean value of CRP at POD3 was highest during the perioperative period with measurement of CRP in both the open and laparoscopic surgery groups. Patients undergoing open surgery had significantly higher CRP levels than those undergoing laparoscopic surgery preoperatively and at POD 1, POD3, and POD7 ($P < 0.0001$; Table 2); cumulative CRP was significantly higher in patients undergoing open surgery than in those undergoing laparoscopic surgery ($P < 0.0001$; Table 2).

Table 2. Perioperative and Cumulative CRP Values in This Cohort.

CRP (mg/dL)	Laparoscopic surgery n = 271 (mean ± SD)	Open surgery n = 269 (mean ± SD)	*P*-value
Preoperative	0.29 ± 0.88	0.93 ± 2.49	**<0.0001**
POD1	5.65 ± 3.27	9.95 ± 5.09	**<0.0001**
POD3	8.17 ± 5.87	11.8 ± 6.84	**<0.0001**
POD7	3.03 ± 4.1	4.8 ± 5.44	**<0.0001**
Cumulative CRP	38.9 ± 25.6	59.9 ± 33.4	**<0.0001**

CRP, C-reactive protein; POD, postoperative day; SD, standard deviation. Bold font indicates statistical significance.

Table 3. Association between Clinicopathological Findings and Cumulative CRP in Patients in This Cohort.

Variables		Cumulative CRP (mean ± SD) Laparoscopic surgery	*P*-value	Cumulative CRP (mean ± SD) Open surgery	*P*-value
Age	<68	33.5 (±22.2)	**0.0011**	60.9 (±35.3)	0.8291
	≥68	44 (±27.5)		58.9 (±31.1)	
Gender	female	31.9 (±23.2)	**<0.0001**	53.3 (±28.5)	**0.018**
	male	44.5 (±26.1)		63.8 (±35.4)	
Serosal invasion	T1 + 2 + 3	38.6 (±25.5)	0.4103	59.4 (±34.3)	0.2318
	T4	44.3 (±27.3)		62.3 (±29.4)	
Lymph node metastasis	absent	38.5 (±25.8)	0.4449	57.4 (±31.5)	0.1721
	present	40 (±25.2)		64.1 (±35.9)	
Histology	well/mod	38.9 (±25.9)	0.4363	58.8 (±32)	0.2731
	por/muc	40.2 (±13.5)		67.6 (±41)	
Lymphatic invasion	absent	39.1 (±27.3)	0.623	57 (±33.5)	0.244
	present	38.7 (±24.1)		61.3 (±33.3)	
Venous invasion	absent	39 (±26.1)	0.924	59.6 (±31.8)	0.8373
	present	38.7 (±24.8)		60.4 (±35.1)	
Location	colon	42 (±25.3)	**0.0015**	62.3 (±33.8)	0.302
	rectum	33.4 (±25.3)		58.4 (±33.1)	
Chemoradiotherapy	no	39 (±25.8)	0.8211	57.9 (±29.9)	0.4626
	yes	34.9 (±19.2)		63.2 (±37.9)	
PIC	absent	33.8 (±21.1)	**<0.0001**	50.3 (±25.3)	**<0.0001**
	present	70.8 (±28.6)		85.4 (±38.6)	
CEA	≤5 ng/mL	37.3 (±25.2)	0.063	57.6 (±30.9)	0.4376
	>5 ng/mL	42.2 (±25.2)		62.8 (±36.1)	

CEA, carcinoembryonic antigen; PIC, postinfectious complication; CRP, C-reactive protein; SD, standard deviation. Median age at surgery was 68 years in this cohort. Bold font indicates statistical significance.

Association between clinicopathological findings and cumulative CRP in open and laparoscopic surgery

The cumulative CRP was significantly higher in male patients and in those with PIC in both the laparoscopic ($P < 0.0001$, $P < 0.0001$, respectively) and open surgery groups ($P = 0.018$, $P < 0.0001$, respectively). By contrast, cumulative CRP was not associated with pathological status such as serosal invasion, lymph node metastasis, tumor grade, and lymphovascular invasion (Table 3).

Association between cumulative CRP and prognosis in patients with CRC who underwent open and laparoscopic surgery

We analyzed the association between cumulative CRP and prognosis according to open and laparoscopic surgery because operative stress differs between operative procedures. In both the open surgery and laparoscopic surgery groups (Figure 2), patients with high cumulative CRP had worse DFS and OS than those with low cumulative CRP (open surgery: $P < 0.0001$, $P < 0.0001$, respectively; laparoscopic

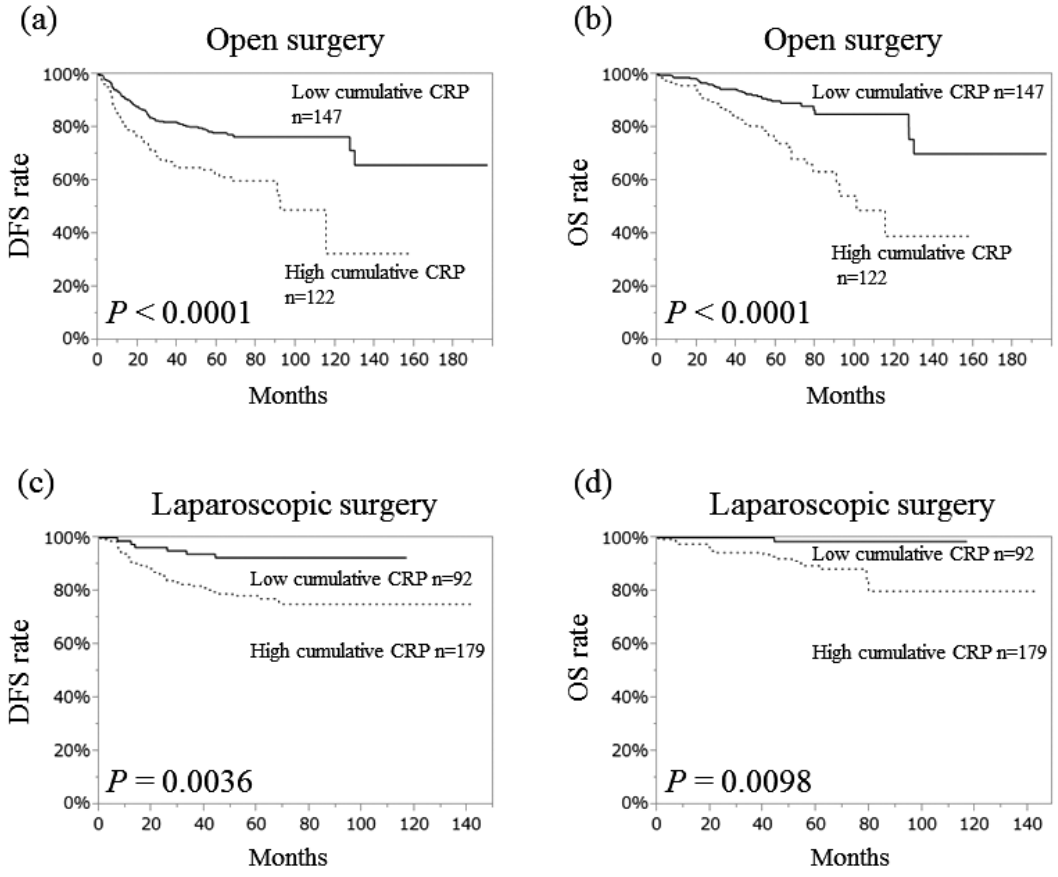

Figure 2. Analysis of the association of cumulative C-reactive protein (CRP) with survival in patients who underwent open or laparoscopic surgery in this cohort. Kaplan–Meier analysis of disease-free survival (DFS) and overall survival (OS) according to cumulative CRP in patients who underwent open (a: DFS, b: OS) or laparoscopic surgery (c: DFS, d: OS). The high cumulative CRP group had CRP levels higher than the cut-off value (open surgery: 57.8; laparoscopic surgery: 24.1). Both DFS and OS in the high cumulative CRP group were significantly lower than those in the low cumulative CRP group.

surgery: P = 0.0036, P = 0.0098, respectively). In the univariate analysis of open surgery, serosal invasion (T4), lymph node metastasis, lymphatic invasion, venous invasion, serum CEA levels (>5 ng/mL), PIC, and high cumulative CRP were associated with poor DFS (Table 4). Furthermore, lymph node metastasis, venous invasion, PIC, and high cumulative CRP were associated with poor OS (Table 4). In multivariate analysis, high cumulative CRP was an independent prognostic factor for both DFS (hazard ratio [HR]: 2.3, 95% confidence interval [CI] 1.44-3.73, P = 0.0005; Table 4) and OS (HR: 3.27, 95% CI 1.84-5.96, P < 0.0001; Table 4). In the univariate analysis of laparoscopic surgery, male sex, CRT, serosal invasion (T4), lymphatic invasion, venous invasion, and high cumulative CRP were associated with poor DFS (Table 5), and older age (>68 years), male sex, and high cumulative CRP were associated with poor OS (Table 5). In multivariate analysis, male sex and high cumulative CRP were independent prognostic factors for both DFS (HR: 2.49, 95% CI 1.1-6.7, P = 0.027; Table 5) and OS (HR: 5.71, 95% CI 1.14-103.8, P = 0.0303; Table 5).

Association between PIC and prognosis in patients with CRC

The cumulative CRP was significantly higher in patients with PIC in this cohort (Table 3). Therefore, we evaluated the association between PIC and prognosis in patients with CRC. In the survival analysis, the PIC group had significantly poorer prognosis than the non-PIC group for both DFS and OS (P < 0.0001, P < 0.0001, respectively; Figure 3).

Prognosis of patients with CRC without PIC, by cumulative CRP level

Next, we evaluated the association between prognosis and cumulative CRP in patients with CRC who did not have PIC. Patients with high cumulative CRP had significantly poorer DFS and OS than those with low cumulative CRP in

Table 4. Cox Proportional-hazards Model Analysis for DFS and OS Predictors in Patients Who Underwent Open Surgery in This Cohort.

DFS

Variables	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Age (≥68)	1.19 (0.78–1.78)	0.4178		
Gender (Male)	0.98 (0.65–1.51)	0.9302		
Tumor location (rectum)	1.28 (0.84–2.01)	0.252		
Chemoradiotherapy (yes)	0.72 (0.46–1.09)	0.1234		
Histology (por/muc)	0.99 (0.53–1.72)	0.9745		
Serosal invasion (T4)	2.35 (1.49–3.62)	**0.0004**	1.54 (0.95–2.45)	0.0789
Lymph node metastasis (positive)	2.67 (1.77–4.06)	**<0.0001**	2.07 (1.31–3.31)	**0.0019**
Lymphatic invasion (positive)	1.79 (1.12–3.02)	**0.0148**	0.97 (0.55–1.76)	0.9143
Venous invasion (positive)	2.17 (1.43–3.36)	**0.0003**	1.51 (0.92–2.52)	0.1052
CEA (>5)	1.82 (1.18–2.88)	**0.007**	1.35 (0.88–2.24)	0.2075
PIC (yes)	2.26 (1.48–3.41)	**0.0002**	1.41 (0.88–2.24)	0.1493
Cumulative CRP (>57.8)	2.43 (1.6–3.73)	**<0.0001**	2.3 (1.44–3.73)	**0.0005**

OS

Variables	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Age (≥68)	1.48 (0.88–2.46)	0.1407		
Gender (Male)	1.05 (0.63–1.81)	0.8557		
Tumor location (rectum)	1.22 (0.72–2.15)	0.473		
Chemoradiotherapy (yes)	0.67 (0.39–1.13)	0.138		
Histology (por/muc)	1.29 (0.62–2.44)	0.4686		
Serosal invasion (T4)	1.73 (0.93–3.03)	0.0798		
Lymph node metastasis (positive)	1.78 (1.07–2.95)	**0.0266**	1.43 (0.84–2.46)	0.1802
Lymphatic invasion (positive)	1.69 (0.94–3.25)	0.0795		
Venous invasion (positive)	1.9 (1.13–3.27)	**0.0143**	1.89 (1.09–3.36)	**0.0217**
CEA (>5)	1.48 (0.86–2.61)	0.1544		
PIC (yes)	2.57 (1.53–4.26)	**0.0005**	1.59 (0.91–2.72)	0.0964
Cumulative CRP (>57.8)	3.48 (2.05–6.14)	**<0.0001**	3.27 (1.84–5.96)	**<0.0001**

DFS, disease-free survival; OS, overall survival; CEA, carcinoembryonic antigen; PIC, postinfectious complication; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval. Median age at surgery was 68 years in this cohort. Bold font indicates statistical significance.

both the open (P = 0.0115, P = 0.0019, respectively; Figure 4a, 4b) and laparoscopic surgery groups (P = 0.0045, P = 0.0103, respectively; Figure 4c, 4d).

Discussion

The interaction between cancer cells and their microenvironment is considered to be an essential component of tumor progression and development of metastasis[21]. This microenvironment consists of inflammatory and immune cells and involves neutrophils and macrophages, carcinoma-associated fibroblasts, environmental conditions such as hypoxia, soluble factors, signaling molecules, and extracellular matrix components[22]. In cancer-bearing status, preoperative CRP reflects systemic inflammation induced by tumor-host interactions[8-10,23]. However, postoperative CRP usually reflects surgical stress and PIC as well as systemic inflammation induced by tumor-host interactions[19,20]. CRP is widely used as an early marker for detecting PICs. CRP levels increase after surgery, with a peak at 48 hours, after which time the values decrease in patients who do not experience postoperative complications[19]. In our study, patients with PIC had higher values of cumulative CRP and poorer prognosis than those without PIC. Several studies have shown that patients with PIC, such as anastomotic leakage and intraabdominal abscess, have poorer oncological prognosis than those without PIC[24,25]. Several hypotheses for the underlying mechanism are the implantation of tumor cells deposited extraluminally upon anastomotic leakage and apoptotic inhibition and proliferation of implanted cancer cells and occult metastasis caused by acute inflammatory response[26-28]. In addition, older patients are more likely to have a higher PIC rate. Therefore, PIC could be associated with poor survival from oncological and physiological standpoints.

Several reports support the hypothesis that the acute in-

Table 5. Cox Proportional-hazards Model Analysis for DFS and OS Predictors in Patients Who Underwent Laparoscopic Surgery in This Cohort.

DFS

Variables	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Age (≥68)	1.06 (0.57–1.94)	0.8623		
Gender (Male)	3.75 (1.83–8.73)	**0.0002**	2.69 (1.26–6.48)	**0.0098**
Tumor location (rectum)	1.49 (0.79–2.74)	0.2056		
Chemoradiotherapy (yes)	4.43 (1.52–10.4)	**0.0095**	6.45 (2.13–16)	**0.0023**
Histology (por/muc)	0.71 (0.04–3.26)	0.7194		
Serosal invasion (T4)	3.51 (1.21–8.17)	**0.0243**	2.01 (0.67–4.89)	0.1932
Lymph node metastasis (positive)	1.75 (0.93–3.21)	0.0834		
Lymphatic invasion (positive)	3.29 (1.65–7.33)	**0.0005**	2.98 (1.37–7.09)	**0.0053**
Venous invasion (positive)	2.59 (1.41–4.88)	**0.0022**	1.46 (0.75–2.93)	0.2708
CEA (>5)	0.89 (0.45–1.69)	0.7388		
PIC (yes)	1.19 (0.48–2.52)	0.6786		
Cumulative CRP (>24.1)	3.34 (1.51–8.83)	**0.0018**	2.49 (1.1–6.7)	**0.027**

OS

Variables	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Age (≥68)	3.17 (1.21–9.82)	**0.0177**	2.85 (1.08–8.86)	**0.033**
Gender (Male)	4.9 (1.63–21.1)	**0.0033**	3.75 (1.23–16.2)	**0.0177**
Tumor location (rectum)	1.04 (0.36–2.69)	0.9351		
Chemoradiotherapy (yes)	n.a.	0.3295		
Histology (por/muc)	n.a.	0.2529		
Serosal invasion (T4)	1.34 (0.07–6.58)	0.7834		
Lymph node metastasis (positive)	1.45 (0.54–3.62)	0.4425		
Lymphatic invasion (positive)	1.77 (0.7–5.05)	0.2324		
Venous invasion (positive)	1.35 (0.52–3.38)	0.5236		
CEA (>5)	1.55 (0.59–3.84)	0.3543		
PIC (yes)	1.12 (0.26–3.35)	0.8634		
Cumulative CRP (>24.1)	8.96 (1.85–161.3)	**0.0029**	5.71 (1.14–103.8)	**0.0303**

DFS, disease-free survival; OS, overall survival; CEA, carcinoembryonic antigen; PIC, postinfectious complication; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval; n.a. not available. Median age at surgery was 68 years in this cohort. Bold font indicates statistical significance.

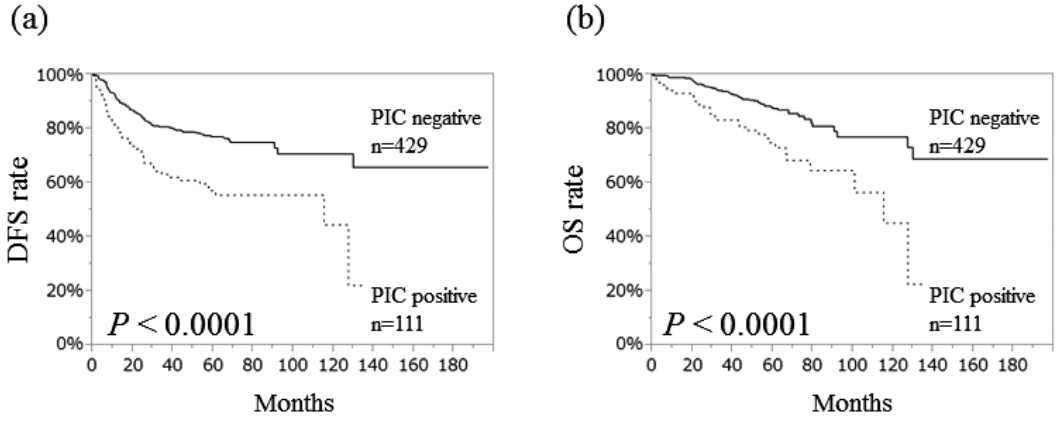

Figure 3. Analysis of the association of postoperative infectious complications (PIC) with survival and cumulative CRP among all patients in this cohort. Kaplan–Meier analysis of disease-free survival (DFS) (a) and overall survival (OS) (b) according to PIC. Both DFS and OS in the PIC group were significantly lower than those in the non-PIC group.

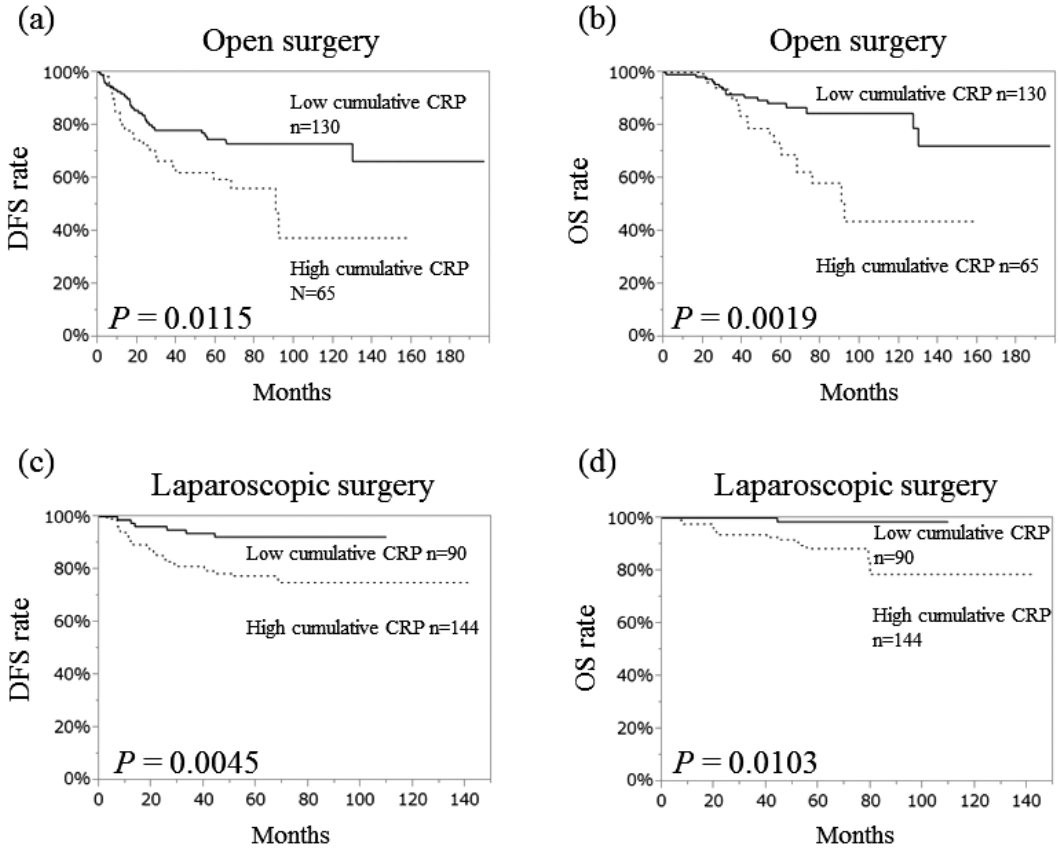

Figure 4. Analysis of the association of cumulative CRP with survival in patients without postoperative infectious complications (PIC) who underwent open or laparoscopic surgery in this cohort. Kaplan–Meier analysis of disease-free survival (DFS) and overall survival (OS) according to cumulative CRP in patients who underwent open (a: DFS, b: OS) or laparoscopic surgery (c: DFS, d: OS). The high cumulative CRP group had higher CRP levels than the cut-off value (open surgery: 57.8; laparoscopic surgery: 24.1). Both DFS and OS in the high cumulative CRP group were significantly lower than those in the low cumulative CRP group.

flammatory response to surgery promotes cancer metastasis, e.g., by stimulating the adhesion of viable circulating cancer cells to the endothelial cell layer owing to proinflammatory cytokines, exposing the underlying extracellular matrix with which the cancer cells can interact, and accelerating development of new metastatic disease through formation of neutrophil extracellular traps[29-32]. Postoperative inflammation is considered to be induced by surgical stress, PIC, and tumor-host interaction. Hence, we assume that the integration of perioperative CRP might more accurately reflect whole inflammation response in the perioperative period compared to one-day CRP, especially when evaluating the inflammatory response of surgical stress and tumor-host interaction. According to the ROC curves, the AUCs of cumulative CRP levels were almost superior or equivalent to the AUCs of each timepoint CRP level, though each AUC was not significantly different (data not shown). Therefore, we designed cumulative CRP as the integration of perioperative CRP. In this study, we evaluated the association between cumulative CRP and oncological outcome in patients with CRC but without PIC. In addition, the high cumulative CRP group had a roughly worse prognosis compared to the low cumulative CRP group in each stage (data not shown). The results showed that patients with higher cumulative CRP had poorer prognosis than those with lower cumulative CRP in both the laparoscopic and open surgery groups, which indicates that the degree of surgical stress might also be a risk factor of poor oncological outcome.

In our study, the group that underwent laparoscopic surgery had lower values of cumulative CRP than that who had open surgery. Most studies also report lower postoperative CRP values with laparoscopic surgery than with open surgery[33]. The lower inflammatory response in laparoscopic surgery compared with open surgery indicates that the laparoscopic procedure is a minimally invasive surgery and is more beneficial to the patient recovery than the conventional open procedure. However, previous randomized controlled trials demonstrated that laparoscopic surgery for CRC did

not differ significantly from open surgery in oncological outcome[34]. Therefore, we hypothesized that the relative inflammatory response in each surgical approach might be associated with oncological outcome and evaluated the association between cumulative CRP and oncological outcome in patients that underwent laparoscopic surgery and open surgery separately. Interestingly, despite the lower surgical stress following laparoscopic surgery, patients with CRC who had higher cumulative CRP values had poorer outcomes than their counterparts.

In this study, high levels of cumulative CRP were an independent prognostic factor for both DFS and OS, although cumulative CRP was not associated with tumor progression factors such as serosal invasion, lymph node metastasis, tumor grade, and lymphovascular invasion. This result shows that perioperative systemic inflammation could worsen long-term outcome after surgery, regardless of the tumor malignant potential. Collectively, cumulative CRP could be a risk factor that is useful in evaluation of aggressive disease as well as conventional tumor staging.

This study has several limitations as this was a single-center, retrospective study with a small sample size. To overcome these limitations, multi-institutional prospective studies with a large sample size are needed.

In conclusion, this is the first study to show that cumulative CRP, which reflects perioperative systemic inflammation caused by surgical stress and PIC, is an independent predictive marker of OS and DFS in patients with CRC who undergo curative surgery. Our findings support that the aggressiveness of perioperative inflammation has a negative impact on oncological outcome in CRC.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

HF drafted the manuscript. HF, AY, HI, TS, TK, MK, HY, YOki, TY, and MO contributed to the collection. HF and YOku analyzed and interpreted the data. HF, YOku, and YT conceived and designed the study. YT edited the manuscript. All authors approved the final manuscript.

Approval by Institutional Review Board (IRB)

The present study was reviewed and approved by the Mie University Institutional Review Board (No. 3203). This study was performed in accordance with the Declaration of Helsinki.

Informed Consent

This project was a retrospective observational study. We offered an opt-out for participants to provide the opportunity to reject participation in the study.

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