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Original Research Article

Prognostic Value of C-reactive Protein-to-albumin Ratio after Curative Resection in Patients with Colorectal Cancer

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Abstract

Objectives: The current retrospective study aimed to evaluate the association between combined preoperative and postoperative C-reactive protein-to-albumin ratio, which is correlated with prognosis in different types of malignancies, and prognosis after curative resection in patients with colorectal cancer.

Methods: This study enrolled 263 patients who underwent curative resection for stage II/III colorectal cancer. C-reactive protein-to-albumin ratio was calculated within 30 days before and 7 days after surgery. Receiver operating characteristic curve analyses were performed to determine the optimal cutoff values of preoperative and postoperative C-reactive protein-to-albumin ratio. The correlations between combined preoperative and postoperative C-reactive protein-to-albumin ratio and prognosis were analyzed.

Results: The cutoff values of preoperative and postoperative C-reactive protein-to-albumin ratio were 0.223 and 0.813, respectively; higher ratios were significantly associated with poor overall survival, based on the Kaplan-Meier curves ($p < 0.001$, $p = 0.003$, respectively). Further, preoperative and postoperative C-reactive protein-to-albumin ratios were correlated with poor progression-free survival ($p < 0.001$, $p = 0.064$, respectively). In the multivariate analysis, combined preoperative and postoperative C-reactive protein-to-albumin ratio was an independent predictor of overall survival and progression-free survival ($p = 0.012$, $p = 0.044$, respectively). Compared with low preoperative and postoperative C-reactive protein-to-albumin ratio, high ratios of that were significantly associated with poor overall survival (hazard ratio = 3.897, $p = 0.006$) and progression-free survival (hazard ratio = 2.130, $p = 0.029$).

Conclusions: Combined preoperative and postoperative C-reactive protein-to-albumin ratio, useful for prognostic prediction, can be a promising prognostic marker after curative resection in patients with colorectal cancer.

Keywords

colorectal cancer, prognosis, C-reactive protein, albumin

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Introduction

Colorectal cancer (CRC) is the third most common malignancy and has the second highest mortality rate[1]. Although there are improvements in surgical procedures and chemotherapy, several patients still have worse outcomes. To further improve treatment outcomes, it is important to not only develop treatment methods but also predict prognosis, which may provide information regarding therapeutic options.

Virchow first discovered the correlation between inflammation and malignancies in 1863[2]. Several studies have shown the detailed mechanisms on the effects of systemic

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inflammatory response on tumor development and progression[3]. Thus, increasing attention has been paid to the development of simple and cost-effective inflammation-based markers, including C-reactive protein-to-albumin ratio (CAR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), Onodera's prognostic nutritional index (PNI), platelet-to-lymphocyte ratio, and Glasgow coma scale score, for predicting prognosis[4].

While most of the inflammation-based markers have evaluated preoperative host status, the number of reports on the association between postoperative inflammation-based markers and prognosis is limited[5-10]. However, the evaluation of postoperative inflammation-based markers after tumor removal may be informative because these markers can reflect different prognostic factors, such as degree of surgical stress and recovery from surgery and the host initial inflammatory status. Furthermore, since preoperative and postoperative inflammation-based markers may be used to evaluate different factors, combined preoperative and postoperative inflammation-based marker can be a good prognostic marker.

CRP (C-reactive protein) reflects systemic inflammatory response, and there are no reports evaluating postoperative CAR. Therefore, this study focused on CAR, which comprises CRP and albumin. Furthermore, CAR is not calculated using blood cell count alone, which is easily affected by age and sex. Hence, it can predict the prognosis of patients with heterogeneous characteristics such as elderly ones[11]. The predictive value of CAR is comparable or superior to that of other inflammation-based markers in different types of malignancies[11-15]. Herein, we evaluate the prognostic significance of perioperative CAR after curative resection in patients with CRC.

Methods

Study patients

The current study was approved by the institutional review board (approval number: 2022GS-028). This study was conducted in accordance with the Helsinki Declaration using opt-out consent. We retrospectively reviewed consecutive patients who underwent elective curative resection for stage II/III CRC at the Department of Surgery of Suita Municipal Hospital between January 2012 and December 2018. Patients with incomplete laboratory data, multiple primary tumors, and those who underwent simultaneous resection of other organs, emergency surgery, and neoadjuvant radiotherapy or chemotherapy were excluded.

Patients were followed-up. That is, they underwent blood tests including carcinoembryonic antigen (CEA) levels every 3 months and chest and abdominal computed tomography scan every 6 months according to the Japanese Society for Cancer of the Colon and Rectum guidelines[16].

Data collection

We collected data on sex, age, body mass index, primary tumor location (rectum: about up to 12 cm from anal verge), tumor size, histological type, CEA level, preoperative and postoperative CAR, pathological T classification, lymph node metastasis, surgical approach, adjuvant chemotherapy, and postoperative complications (i.e., ≥ grade 2 complications within 30 days of surgery based on the Clavien-Dindo classification system[17]). Open conversion from laparoscopic surgery included open surgery as it could not be determined whether conversion was planned or unexpected due to the retrospective nature. Blood tests were conducted within 30 days before and 7 days after surgery. CAR was calculated as CRP levels divided by serum albumin levels.

Statistical analysis

Continuous variables were presented as median and range. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of preoperative and postoperative CAR. Categorical variables were compared using the Fisher's exact probability test, and continuous variables were compared using the Mann-Whitney U test. Kaplan-Meier curves and log-rank tests were utilized to analyze survival data. A multivariate analysis was performed using the Cox proportional hazard model to determine the predictive factors of overall survival (OS) and relapse-free survival (RFS). P values of <0.05 were considered significant. Statistical analyses were conducted using JMP software (version 13; SAS Institute, Cary, NC, the USA).

Results

Clinicopathological characteristics of the participants

Table 1 shows the characteristics of 263 patients at a median follow-up period of 50.0 months. The current study comprised 146 male and 117 female, with a median age of 72 years. The median preoperative and postoperative CAR levels were 0.055 and 0.397, respectively. In total, 120 patients had positive lymph node metastasis, and 143 did not. Moreover, 51 (19.4%) patients presented with postoperative complications. There was an extremely low correlation between the preoperative and postoperative CAR ($r = 0.127$, $p = 0.040$) (Figure 1).

Correlations between preoperative and postoperative CAR and clinicopathological characteristics

According to the ROC analyses, the cutoff values of preoperative and postoperative CAR were 0.223 and 0.813, respectively (Figure 2). Based on these values, the participants were classified under the high and low CAR groups preop-

Table 1. Clinicopathological Characteristics of the Patients.

Characteristics of the patients	Total n = 263
Sex, n (%)	
Male	146 (55.5)
Female	117 (44.5)
Age (range), years	72 (41–100)
BMI (range), kg/m^2	21.97 (13.31–36.96)
Primary tumor location, n (%)	
Colon	228 (86.7)
Rectum	35 (13.3)
Tumor size (range), mm	50 (15–130)
Histological type, n (%)	
Well/moderately differentiated	241 (91.6)
Others	22 (8.4)
CEA level, ng/mL	
<5	147 (56.3)
>5	114 (43.7)
Preoperative CAR (range)	0.054 (0.039–7.919)
Postoperative CAR (range)	0.397 (0.050–6.748)
Tumor depth, n (%)	
T1–3	212 (80.6)
T4	51 (19.4)
Lymph node metastasis, n (%)	
Negative	120 (45.6)
Positive	143 (54.4)
Surgical approach, n (%)	
Open	35 (13.3)
Laparoscopic	228 (86.7)
Adjuvant chemotherapy, n (%)	
No	148 (56.3)
Yes	115 (43.7)
Complications (>grade 2 based on the CD classification system)	
Absent	212 (80.6)
Present	51 (19.4)

BMI, body mass index; CEA, carcinoembryonic antigen; CAR C-reactive protein-to-albumin ratio

erative and postoperatively. A high preoperative CAR was associated with a tumor size of ≥ 50 mm ($p < 0.001$), tumor depth (T4) ($p = 0.006$), open surgery ($p = 0.001$), and postoperative complication ($p = 0.017$). Among the 35 open surgery patients, 18 patients were open conversion from laparoscopic surgery. A high postoperative CAR was correlated with age ≥75 years ($p = 0.001$), primary tumor location (rectum) ($p = 0.030$), open surgery ($p = 0.030$), and postoperative complication ($p < 0.001$) (Table 2).

Survival analysis according to preoperative and postoperative CAR

Based on the survival curves, the high preoperative CAR group had significantly lower 5-year OS and RFS rates than the low preoperative CAR group (69.5% vs. 88.0%; $p < 0.001$; 55.4% vs. 75.4%; $p = 0.003$, respectively) (Figure 3a, b). The high postoperative CAR group had lower OS and PFS rates than the low postoperative CAR group (72.7% vs. 87.1%; $p < 0.001$; 63.5% vs. 73.8%; $p = 0.064$, respectively) (Figure 3c, d).

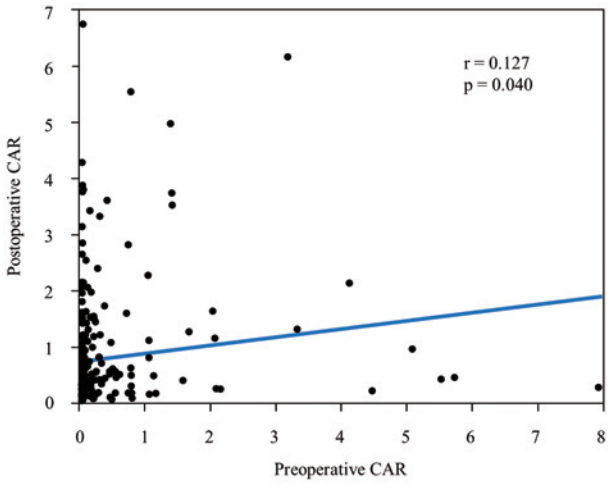

Figure 1. Correlation between preoperative and postoperative CAR. CAR C-reactive protein-to-albumin ratio

Survival analysis according to the combined preoperative and postoperative CAR

According to the combined preoperative and postoperative CAR, the patients were divided into three groups, which were as follows: low CAR group (both preoperative and postoperative patients with low CAR), intermediate CAR group (preoperative patients with high CAR and postoperative patients with low CAR or preoperative patients with low CAR and postoperative patients with high CAR), and high CAR group (both preoperative and postoperative patients with high CAR). Table 3 shows the association between the combined preoperative and postoperative CAR and clinicopathological features. Age ($p = 0.005$), tumor size ($p = 0.005$), surgical approach ($p < 0.001$), and postoperative complication ($p < 0.001$) were associated with the combined preoperative and postoperative CAR. Figure 4 shows the survival curves of OS and PFS. The high CAR group had a lower OS than the low CAR group and intermediate CAR groups ($p < 0.001$, $p = 0.0130$, respectively). The intermediate CAR group had a lower OS than the low CAR group ($p = 0.006$). The high CAR group had a lower PFS than the low and intermediate CAR groups ($p < 0.001$, $p = 0.041$, respectively).

Predictive factors of prognosis

Table 4 shows the correlations between clinicopathological factors and OS. According to the univariate analysis, age ($p = 0.002$), lymph node metastasis ($p = 0.028$), postoperative complications ($p = 0.016$), and combined preoperative

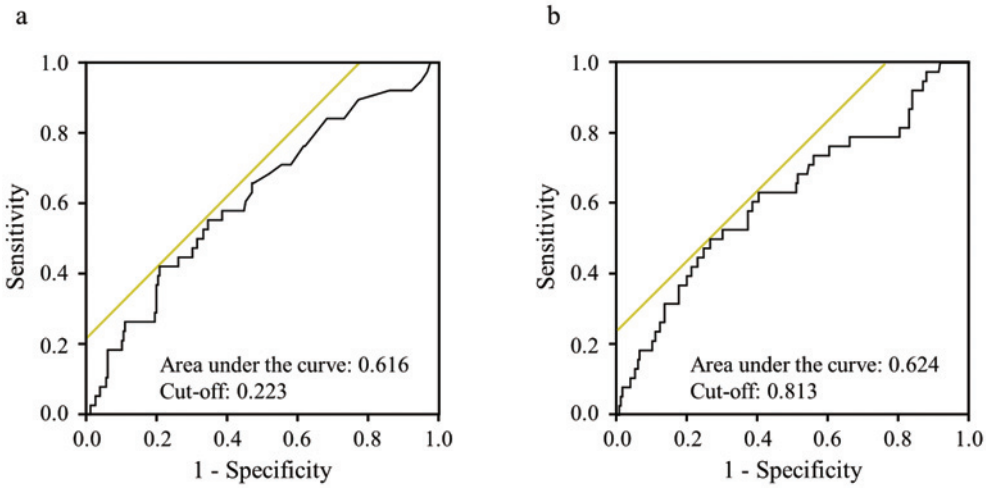

Figure 2. Receiver operating characteristics curves of preoperative (a) and postoperative (b) CAR of overall survival in patients with colorectal cancer after curative resection. CAR C-reactive protein-to-albumin ratio

and postoperative CAR ($p < 0.001$) were significantly associated with OS. Multivariate analysis revealed that age ($p = 0.007$), lymph node metastasis ($p = 0.017$), and combined preoperative and postoperative CAR ($p = 0.013$) were significantly correlated with OS. Table 5 shows the correlations between clinicopathological factors and PFS. According to the univariate analysis, age ($p = 0.029$), CEA level ($p < 0.001$), lymph node metastasis ($p = 0.003$), and combined preoperative and postoperative CAR ($p = 0.005$) were significantly associated with PFS. Multivariate analysis revealed that CEA levels ($p = 0.005$), lymph node metastasis ($p = 0.005$), and combined preoperative and postoperative CAR ($p = 0.044$) were significantly correlated with PFS.

Discussion

The current study investigated the correlation between CAR and prognosis after curative resection for stage II/III CRC. Results showed that a high preoperative and postoperative CAR was correlated with poor prognosis. Furthermore, combined preoperative and postoperative CAR could stratify prognosis and better extract populations with poor or favorable prognosis. To the best of our knowledge, this is the first study that assessed the prognostic value of combined preoperative and postoperative CAR.

CAR is an inflammation-based marker calculated using CRP and serum albumin concentrations, which are easy-to-measure and cost-effective in clinical settings. This marker has been used in acute cases such as medical admission and death in patients with sepsis[18,19]. However, recently, CAR was found to have a prognostic value in different types of malignant tumors[11-15,20]. Although the actual mechanisms for the association between CAR and prognosis are not clearly understood, the possible explanations are as follows: First, elevated CRP levels are associated with poor prognosis in different types of malignancies[21-24]. CRP is an acute-phase protein synthesized in hepatocytes and is regulated by inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor[25]. These inflammatory cytokines promote tumor growth, invasion, and metastasis. Therefore, elevated CRP levels indicate the production of inflammatory cytokines and, consequently, poor prognosis. Second, decreased albumin levels are associated with poor prognosis[26-28]. Serum albumin, which is the most abundant protein in the plasma protein, represents host nutrition. Hypoalbuminemia reflects not only undernourishment but also nutritional impairment, which is associated with inflammatory and immunosuppressive conditions[29]. These conditions enhance cancer progression, and they are associated with decreased quality of life[27]. Moreover, if systemic inflammatory response occurs, which then causes decreased albumin levels, the CRP level increases[15]. Taken together, preoperative CAR is correlated with prognosis by reflecting not only inflammation but also immunonutritional status. As previously reported, the current study showed that high preoperative CAR was associated with poor prognosis.

Recent studies have focused on the association between not only preoperative but also postoperative inflammatory status and prognosis. The underlying mechanism for the effect of postoperative inflammation on cancer prognosis has not been validated yet. However, this phenomenon has possible explanations. First, surgery-related inflammation is involved in immunosuppression, prothrombotic change, and imbalance of pro-/anti-tumorigenic cytokine that influences tumor progression[30-32]. Changes in host status, which is

Table 2. Association between the Preoperative and Postoperative C-Reactive Protein-to-Albumin Ratio and Clinicopathological Characteristics.

	Preoperative CAR			Postoperative CAR		
	High CAR group (n = 63)	Low CAR group (n = 200)	*p* value	High CAR group (n = 78)	Low CAR group (n = 185)	*p* value
Characteristics of the participants						
Sex, n (%)			0.565			0.136
Male	37 (58.7)	109 (54.5)		49 (62.8)	97 (52.4)	
Female	26 (41.3)	91 (45.5)		29 (37.2)	88 (47.6)	
Age (years), n (%)			0.148			0.001
<75	29 (46.0)	114 (57.0)		30 (38.5)	113 (61.1)	
>75	34 (54.0)	86 (43.0)		48 (61.5)	72 (38.9)	
BMI (kg/m^2), n (%)			0.291			1.000
<25	53 (84.1)	155 (77.5)		62 (79.5)	146 (78.9)	
>25	10 (15.9)	45 (22.5)		16 (20.5)	39 (21.1)	
Primary tumor location, n (%)			0.673			0.030
Colon	56 (88.9)	172 (86.0)		62 (79.5)	166 (89.7)	
Rectum	7 (11.1)	28 (14.0)		16 (20.5)	19 (10.3)	
Tumor size (mm), n (%)			<0.001			0.496
<50	13 (20.6)	101 (50.8)		31 (39.7)	83 (45.1)	
>50	50 (79.4)	98 (49.2)		47 (60.3)	101 (54.9)	
Histological type, n (%)			0.747			0.627
Well/moderately differentiated	57 (90.5)	184 (92.0)		73 (93.6)	168 (90.8)	
Others	6 (9.5)	16 (8.0)		5 (6.4)	17 (9.2)	
CEA level (ng/mL), n (%)			0.187			1.000
<5	30 (48.4)	117 (58.8)		43 (55.8)	104 (56.5)	
>5	32 (51.6)	82 (41.2)		34 (44.2)	80 (43.5)	
Tumor depth, n (%)			0.006			0.609
T1–3	43 (68.3)	169 (84.5)		61 (78.2)	151 (81.6)	
T4	20 (31.7)	31 (15.5)		17 (21.8)	34 (18.4)	
Lymph node metastasis, n (%)			0.247			0.416
Negative	33 (52.4)	87 (43.5)		39 (50.0)	81 (43.8)	
Positive	30 (47.6)	113 (56.5)		39 (50.0)	104 (56.2)	
Surgical approach, n (%)			0.001			0.030
Open	17 (27.0)	18 (9.0)		16 (20.5)	19 (10.3)	
Laparoscopic	46 (73.0)	182 (91.0)		62 (79.5)	166 (89.7)	
Adjuvant chemotherapy, n (%)			0.194			0.104
No	40 (63.5)	108 (54.0)		50 (64.1)	98 (53.0)	
Yes	23 (36.5)	92 (46.0)		28 (35.9)	87 (47.0)	
Complications (>grade 2 based on the CD classification system), n (%)			0.017			<0.001
Absent	44 (69.8)	168 (84.0)		45 (57.7)	167 (90.3)	
Present	19 (30.2)	32 (16.0)		33 (42.3)	18 (9.7)	

BMI, body mass index; CEA, carcinoembryonic antigen; CAR, C-reactive protein-to-albumin ratio

favorable for the development of tumor triggered by inflammatory response, activates residual tumor cell growth during the postoperative period. Second, inflammatory response itself enhances cancer stem cell proliferation[2,33]. Inflammation-related tumor effects may worsen prognosis, and this then supports the notion that postoperative complication and elevated postoperative CRP levels are correlated with poor prognosis[34-39]. Based on these findings, we investigated the association between postoperative CAR and prognosis. Results showed that high postoperative CAR was associated with poor prognosis. Further, it was associated with old age, primary tumor location (rectum), open surgery, and postoperative complication. This finding suggests that high postoperative CAR could predict poor prognosis as a result of reflecting a prolonged higher inflammatory state induced by surgical stress, slow recovery, and additional stress.

Furthermore, combined preoperative and postoperative

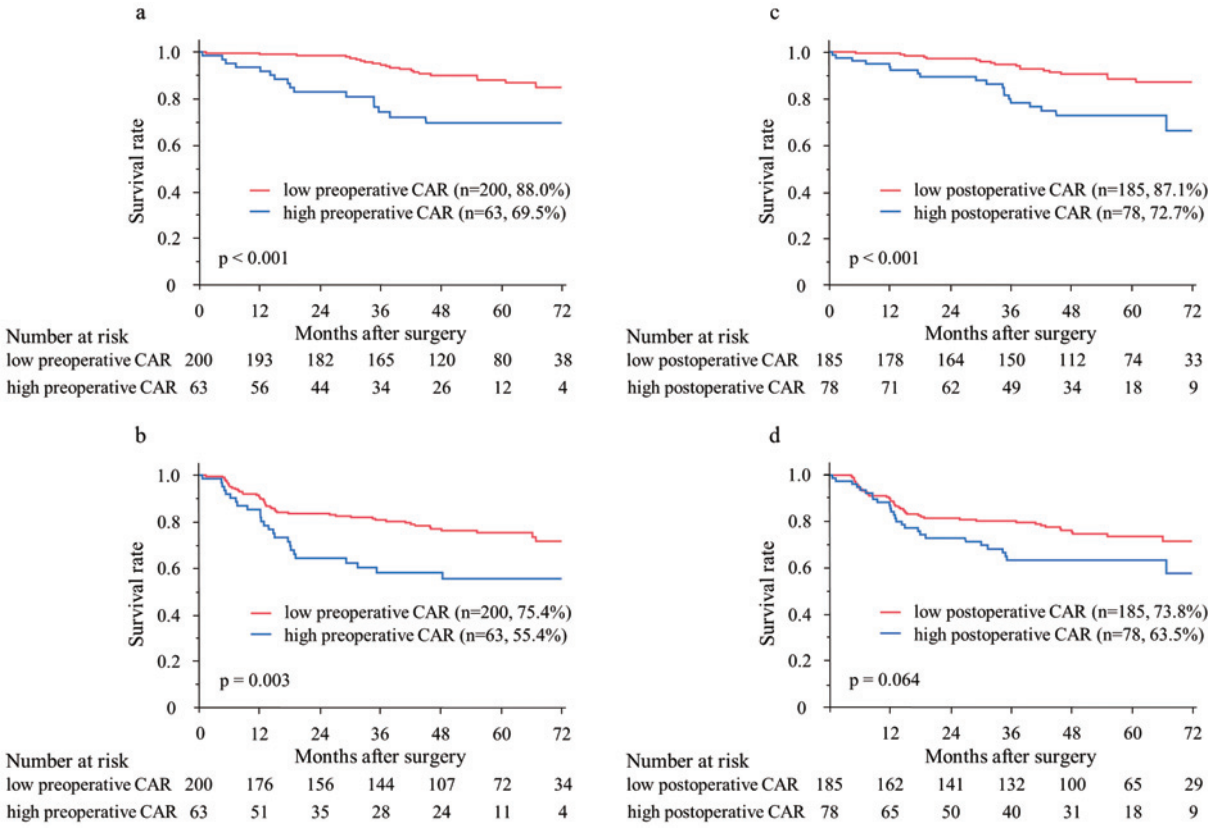

Figure 3. Overall survival (a) and progression-free survival (b) according to preoperative CAR and overall survival (c) and progression-free survival (d) according to postoperative CAR. CAR C-reactive protein-to-albumin ratio

CAR could stratify prognosis. Notably, stratification is good in extracting poor and favorable prognosis. Based on preoperative CAR assessment alone, 200 patients presented with a low CAR and 63 with a high CAR. The 5-year OS rates were 88.0% and 69.5%, respectively. The 5-year-PFS rates were 75.4% and 55.4%, respectively. Meanwhile, according to the combined preoperative and postoperative CAR assessment, 149 patients were included in the low CAR group and 27 in the high CAR group. The 5-year OS rates were 89.0% and 57.1%, respectively. The 5-year-PFS rates were 76.5% and 47.2%, respectively. Increased discriminability may be achieved by adding an intermediate CAR group. Based on the low preoperative CAR and the high postoperative CAR, these patients developed inflammation postoperatively. Meanwhile, the high preoperative CAR and the low postoperative CAR suggested that the patients were free from tumor-related inflammation via tumor elimination. In fact, the intermediate CAR group is between the low and high CAR groups based on the Kaplan-Meier curves. Several studies have evaluated the association between changes in the levels of perioperative inflammation-based markers (including PNI, LMR, and NLR) and prognosis[5-10]. However, the current study first showed the association between combined preoperative and postoperative CAR and prognosis.

Previous reports have commonly evaluated postoperative markers at approximately 1 month after surgery. This could represent the host initial status without surgical stress and tumor influence. Murakami et al. and Miyatani et al., who evaluated the inflammatory status 1 month after surgery, showed a positive correlation between preoperative and postoperative markers in PNI (r = 0.59) and NLR (r = 0.38)[7,8], respectively. Even after tumor resection, the characteristics of postoperative inflammatory status may not differ significantly from the preoperative inflammatory status. In contrast, evaluation 7 days after surgery in the current study could strongly reflects the degree of surgical stress rather than nature of host status. The current study had only an extremely weak correlation between preoperative and postoperative CAR (r = 0.13). Hence, the combination of preoperative and postoperative CAR can be a combination of two factors with different characteristics. The best timing for evaluation or whether the timing differs based on the marker should still be determined. However, combining early postoperative CAR with preoperative CAR has good prognostic predictability. Predicting prognosis in the early postoperative period could be advantageous for subsequent treatments such as adjuvant chemotherapy selection.

Recent molecular biological approaches, such as ctDNA and immunoscoring, likely play an important role in predict-

Table 3. Associations between Combined Preoperative and Postoperative C-Reactive Protein-to-Albumin Ratio and Clinicopathological Characteristics.

	Low CAR group	Intermediate CAR group	High CAR group	*p* value
Sex, n (%)				0.350
Male	78 (52.4)	50 (57.5)	18 (66.7)	
Female	71 (47.6)	37 (42.5)	9 (33.3)	
Age (years), n (%)				0.005
<75	93 (62.4)	41 (47.1)	9 (33.3)	
>75	56 (37.6)	46 (52.9)	18 (66.7)	
BMI (kg/m^2), n (%)				0.134
<25	113 (75.8)	75 (86.2)	20 (74.1)	
>25	36 (24.2)	12 (13.8)	7 (25.9)	
Primary tumor location, n (%)				0.521
Colon	132 (88.6)	74 (85.1)	22 (81.5)	
Rectum	17 (11.4)	13 (14.9)	5 (18.5)	
Tumor size (mm), n (%)				0.005
<50	77 (52.0)	30 (34.5)	7 (25.9)	
>50	71 (48.0)	57 (65.5)	20 (74.1)	
Histological type, n (%)				0.535
Well/moderately differentiated	135 (90.6)	82 (94.3)	24 (88.9)	
Others	14 (9.4)	5 (5.8)	3 (11.1)	
CEA level (ng/mL), n (%)				0.127
<5	84 (56.8)	53 (60.9)	10 (38.5)	
>5	64 (43.2)	34 (39.1)	16 (61.5)	
Tumor depth, n (%)				0.075
T1–3	126 (84.6)	68 (78.2)	18 (66.7)	
T4	23 (15.4)	19 (21.8)	9 (33.3)	
Lymph node metastasis, n (%)				0.325
Negative	62 (41.6)	44 (50.6)	14 (51.9)	
Positive	87 (58.4)	43 (49.4)	13 (48.1)	
Surgical approach, n (%)				<0.001
Open	11 (7.4)	15 (17.2)	9 (33.3)	
Laparoscopic	138 (92.6)	72 (82.7)	18 (66.7)	
Adjuvant chemotherapy, n (%)				0.108
No	78 (52.4)	50 (57.5)	20 (74.1)	
Yes	71 (47.6)	37 (42.5)	7 (25.9)	
Complications (>grade 2 based on the CD classification system), n (%)				<0.001
Absent	137 (92.0)	61 (70.1)	14 (51.9)	
Present	12 (8.0)	26 (29.9)	13 (48.1)	

BMI, body mass index; CEA, carcinoembryonic antigen; CAR, C-reactive protein-to-albumin ratio

ing recurrence[40,41]. Particularly, research on ctDNA-based postoperative adjuvant chemotherapy selection is rapidly progressing[42-44]. Preclinical studies of these molecular approaches have determined the relationship between recurrence and its predictors. Conversely, as mentioned above, it is difficult to elucidate the mechanism by which CAR influences prognosis because CAR is considered a complex indicator of host immune and inflammatory status. However, considering that recurrence may result from multiple factors, such as host, tumor, and surgical factors, CAR may serve as a complement to molecular biological approaches. Furthermore, CAR is particularly useful in low-income countries due to its affordability.

The current study had several limitations. First, it was retrospective in nature, and a relatively small number of patients from a single center were included. Second, underlying diseases likely to affect blood test results, including liver cirrhosis, chronic renal failure, and infections, were not taken into consideration. Third, blood test on postoperative day 7 might not be the best for predicting prognosis. Yamamoto et al. showed that the highest CRP level after surgery had the highest area under the ROC curve and was

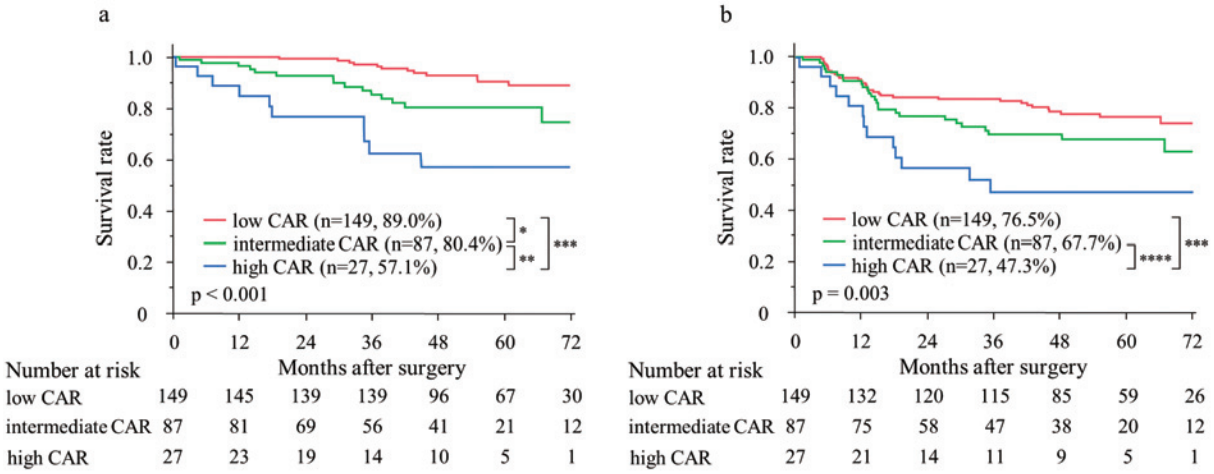

Figure 4. Overall survival (a) and progression-free survival (b) according to combined preoperative and postoperative CAR (*, p = 0.006; **, p = 0.013; ***, p < 0.001; ****, p = 0.041). CAR C-reactive protein-to-albumin ratio

Table 4. Univariate and Multivariate Analyses of the Predictive Factors of Overall Survival.

Characteristics of the participants	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex (male)	1.234	0.640–2.379	0.530			
Age (>75 years)	3.057	1.531–6.103	0.002	2.726	1.313–5.661	0.007
BMI (>25 mg/m^2)	1.478	0.730–2.992	0.278			
Primary tumor location (rectum)	1.427	0.627–3.250	0.397			
Tumor size (>50 mm)	1.063	0.551–2.052	0.856			
Histological type (others)	1.335	0.265–2.117	0.586			
CEA level (>5 ng/mL)	1.792	0.928–3.461	0.082	1.640	0.792–3.393	0.183
Tumor depth (T4)	1.096	0.481–2.497	0.827			
Lymph node metastasis (positive)	2.258	1.093–4.666	0.028	2.520	1.181–5.376	0.017
Surgical approach (open)	1.987	0.908–4.347	0.089	1.140	0.450–2.883	0.783
Adjuvant chemotherapy (no)	1.525	0.784–2.967	0.214			
Complications	2.327	1.169–4.635	0.016	1.744	0.778–3.906	0.177
Combined CAR						0.013
Low CAR	1.000	Reference	<0.001	1.000	Reference	
Intermediate CAR	2.731	1.276–5.845	0.010	2.638	1.153–6.033	0.022
High CAR	7.025	3.017–16.357	<0.001	3.897	1.470–10.330	0.006

BMI, body mass index; CEA, carcinoembryonic antigen; CAR, C-reactive protein-to-albumin ratio

closely associated with poor prognosis compared with other measurement timings[45]. Therefore, in the current study, the highest CRP during the postoperative period may be more reliable than that on postoperative day 7. Therefore, further investigations including the timing of postoperative blood test should be conducted to validate the study results.

Conclusion

Combined preoperative and postoperative CAR can be a prognostic predictor after curative resection in patients with CRC. Preoperative CAR may represent host immunonutritional status under tumoral conditions. Meanwhile, postoperative CAR can mainly reflect surgery-related stress. Combined preoperative and postoperative CAR can be obtained easily and a useful biological marker with consideration of long-term outcomes.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

K Tamai: study conception and design, acquisition of

Table 5. Univariate and Multivariate Analyses of the Predictive Factors of Progression-Free Survival.

Characteristics of the participants	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex (male)	1.210	0.759–1.929	0.423			
Age (>75 years)	1.676	1.055–2.663	0.029	1.602	0.994–2.584	0.053
BMI (>25 mg/m^2)	1.403	0.838–2.347	0.198			
Primary tumor location (rectum)	1.145	0.617–2.127	0.668			
Tumor size (>50 mm)	1.145	0.716–1.830	0.571			
Histological type (others)	1.052	0.456–2.427	0.906			
CEA level (>5 ng/mL)	2.218	1.384–3.557	<0.001	2.005	1.232–3.263	0.005
Tumor depth (T4)	1.506	0.884–2.566	0.132			
Lymph node metastasis (positive)	2.151	1.304–3.547	0.003	2.069	1.242–3.447	0.005
Surgical approach (open)	1.386	0.746–2.575	0.302			
Adjuvant chemotherapy (No)	1.126	0.708–1.790	0.616			
Complications	1.403	0.815–2.415	0.222			
Combined preoperative and postoperative CAR			0.005			0.044
Low CAR	1.000	Reference		1.000	Reference	
Intermediate CAR	1.480	0.887–2.468	0.133	1.640	0.974–2.762	0.063
High CAR	2.901	1.525–5.518	0.001	2.130	1.079–4.201	0.029

BMI, body mass index; CEA, carcinoembryonic antigen; CAR, C-reactive protein-to-albumin ratio

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