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Preoperative C-reactive Protein as a Prognostic Factor in Stage IV Colorectal Cancer

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Background: A prognosis for stage IV colorectal cancer is generally poor. As a result, the development of an appropriate treatment strategy for each individual with this disease within a limited time frame is important. Few studies have been made of C-reactive protein (CRP) in stage IV cases of colorectal cancer, so it is unclear whether CRP is a useful prognostic marker for this disease. Thus, the purpose of this study was to clarify the relationship between the preoperative CRP level and the prognosis of stage IV colorectal cancer.

Patients and methods: Between April 2007 and December 2015, a total of 384 patients with stage IV colorectal cancer who underwent primary resection were included. Patients were divided into high (HCG) and low (LCG) CRP groups based on a preoperative CRP cutoff value of 1.0 mg/dL. Postoperative short- and long-term results were examined retrospectively.

Results: The 5-year survival rate was 24.6% for HCG and 36.7% for LCG, indicating the survival rate for HCG was lower. The study was limited to patients who were unable to undergo R0 surgery. Preoperative CEA levels were higher in HCG, whereas the postoperative chemotherapy induction rate was lower. HCG also showed a significantly lower survival rate than LCG. Multivariate analysis showed that CRP levels above 1.0 mg/dL, poorly differentiated histopathology, and the absence of chemotherapy were risk factors affecting overall survival.

Conclusion: These results suggest that the preoperative CRP level may be a useful biomarker for the prognosis of incurable stage IV colorectal cancer.

Key words: CRP – Colorectal cancer – Stage IV

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Treatment outcomes for stage IV colorectal cancer are generally poor. For example, in unresectable colorectal cancer, the median survival time without drug therapy is about 8 months.[1] Recent advances in drug therapy have extended median survival time to more than 30 months, although this disease remains difficult to cure in most patients.[2–4] Because of a limited time with which to act, it is extremely important to formulate an appropriate treatment strategy. However, to date, the prognostication of each patient with stage IV colorectal cancer is thought to be difficult.

A high C-reactive protein (CRP) value in a preoperative examination is suggested to be a poor prognostic factor in various malignant tumors such as gastric,[5] lung,[6] pancreatic,[7,8] and colon cancers.[9] However, most of these reports are on radically treated cases, with few reports on stage IV cases.[10–14] It is therefore unclear whether the CRP level can be a useful prognostic marker for stage IV colorectal cancer. In addition, stage IV colorectal cancer has a wide variety of medical conditions, including the metastatic organs involved, the number of metastases, and whether it is curable or incurable. The purpose of this study is to clarify the relationship between preoperative CRP levels and the prognosis of stage IV colorectal cancer.

Patients and Methods

Between April 2007 and December 2015, a total of 384 patients with stage IV colorectal cancer underwent primary resection at Saitama Medical University International Medical Center. All study participants provided their informed consent. The study design was approved by the Ethics Committee of Saitama Medical University International Medical Center (no. 19-149). All patients were monitored using a standard Japanese postoperative surveillance program. Patients were divided into either a high CRP group (HCG) with preoperative CRP values of 1.0 mg/dL, or a low CRP group (LCG). Operative outcomes included surgical approach, operating time, blood loss, whether or not an R0 surgical resection was possible, and histopathologic diagnosis. We also assessed postoperative complications, and postoperative hospital stays as short-term clinical outcomes. Five-year cancer-specific and overall survival rates served as long-term oncologic outcomes. In this study, short- and long-term outcomes in HCG and LCG were compared retrospectively.

Table 1 Clinical characteristics in all patients

	High CRP group	Low CRP group	*P* value
n	107	277	
Sex, n (%)			
Male	73 (68.2)	172 (62.1)	
Female	34 (31.8)	105 (37.9)	0.262
Age, y	67.27 ± 10.18	65.39 ± 11.05	0.136
Double cancers, (%)			
Yes	8 (7.5)	22 (7.9)	
No	99 (92.5)	255 (92.1)	0.879
Multiple cancers, n (%)			
Yes	9 (8.4)	19 (6.9)	
No	98 (91.6)	258 (93.1)	0.600
ASA–PS, n (%)			
1	41 (38.3)	103 (37.5)	
2	51 (47.7)	147 (53.5)	
3	15 (14.0)	25 (9.1)	0.317
Previous abdominal surgery, n (%)			
Yes	34 (31.8)	101 (36.5)	
No	73 (68.2)	176 (63.5)	0.389
CEA value 5.0 ng/mL, n (%)			
≥5.0 ng/mL	91 (85.0)	197 (71.1)	
<5.0 ng/mL	16 (15.0)	80 (28.9)	0.005
BMI, kg/m^2	22.21 ± 3.83	22.54 ± 3.55	0.404

All statistical analyses were performed using the SPSS software package (SPSS version 25: IBM, Tokyo, Japan). For statistical analysis, we performed χ^2 and Mann-Whitney U tests to examine differences between the two groups. The cumulative survival rate was analyzed with Kaplan-Meier and log-rank tests. $P < 0.05$ was considered a statistically significant difference.

Results

Patient backgrounds are shown in Table 1. There were 107 cases of HCG and 277 cases of LCG. HCG consisted of 73 male and 34 female patients, whereas LCG was made up of 172 males and 105 females. The average ages in each group were 67 and 65 years, respectively. There were no significant differences between HCG and LCG in terms of age, sex, the presence or absence of double or multiple cancers, preoperative American Society of Anesthesiologists physical status (ASA-PS), body mass index (BMI), and history of abdominal surgery. Only preoperative carcinoembryonic antigen (CEA) values were significantly higher in HCG. Table 2 shows short-term postoperative outcomes. A significant difference between HCG and LCG in the rate of laparoscopic surgery, operation time, blood loss, postoperative complication rate, and postoperative hospital stay was not observed. A difference in

Table 2 Short-term outcomes in all patients

	High CRP group	Low CRP group	*P* value
n	107	277	
Laparoscopic surgery, n (%)			
Yes	62 (57.9)	189 (68.2)	
No	45 (42.1)	88 (31.8)	0.058
Operation time, min	216.11 ± 90.24	228.89 ± 85.68	0.064
Blood loss, mL	196.71 ± 332.67	145.70 ± 281.87	0.181
Postoperative complication			
Clavien-Dindo Grade ≥II, n (%)			
Yes	19 (17.8)	42 (15.2)	
No	88 (82.2)	235 (84.8)	0.533
Urination disorder (self-catheterization), n (%)			
Yes	3 (2.8)	6 (2.2)	
No	104 (97.2)	271 (97.8)	0.711
Postoperative hospital stay, days	11.30 ± 9.67	10.96 ± 13.53	0.732
R0 surgical resection, n (%)			
Yes	18 (16.8)	104 (37.5)	
No	89 (83.2)	173 (62.5)	<0.001
Histopathology, n (%)			
Well, moderate	92 (86.0)	247 (89.2)	
Poor, mucinous	15 (14.0)	30 (10.8)	0.384
Lymphatic invasion, n (%)			
Positive	62 (57.9)	159 (57.4)	
Negative	45 (42.1)	118 (42.6)	0.952
Venous invasion, n (%)			
Positive	90 (84.1)	244 (88.1)	
Negative	17 (15.9)	33 (11.9)	0.259
Tumor depth, n (%)			
T1–T3	64 (59.8)	185 (66.8)	
T4	43 (40.2)	92 (33.2)	0.199
Lymph node metastasis, n (%)			
Positive	82 (76.6)	222 (80.1)	
Negative	25 (23.4)	55 (19.9)	0.504
Peritoneal dissemination, n (%)			
Positive	26 (24.3)	53 (19.1)	
Negative	81 (75.7)	224 (80.9)	0.262

histopathologic findings between these 2 groups was also not found. However, the number of cases with an R0 surgical resection of distant metastasis was significantly smaller in HCG. Figure 1 shows a Kaplan-Meier survival curve. The 3-year survival rate was 33.9% for HCG and 49.7% for LCG, whereas the 5-year survival rate was 24.6% for HCG and 36.7% for LCG. This indicated a significantly lower survival rate for HCG ($P < 0.001$). Multivariate analysis of factors affecting the survival rate showed that a CRP value 1.0 (hazard ratio [HR], 0.718; 95% confidence interval [CI], 0.54–0.954; $P = 0.022$), poor histopathologic type (HR, 0.458; 95% CI, 0.314–0.667; $P < 0.001$), positive venous invasion (HR, 0.602; 95% CI, 0.389–0.931; $P = 0.023$), and whether an R0 surgical resection was undertaken (HR, 0.19; 95% CI, 0.132–0.274; $P < 0.001$) were risk factors (Table 3).

In the present study, an R0 surgical resection was performed in 122 cases (31.8%). Eighteen cases (16.8%) had an R0 resection in HCG, and 104 cases (37.5%) in LCG. The proportion of R0 resections was significantly higher in LCG. The background and short-term postoperative outcomes of patients with an R0 resection are shown in Tables 4 and 5. A significant difference between HCG and LCG in background factors, including preoperative CEA value, was not noted. In terms of surgical treatment, the proportion of laparoscopic surgeries was lower in HCG. Accordingly, the amount of estimated blood loss was also larger in HCG. However, a significant difference was not noted between the 2 groups in regard to the postoperative complication rate, the length of postoperative hospital stays, and histopathologic evaluation. As for long-term survival, there was no significant difference in overall

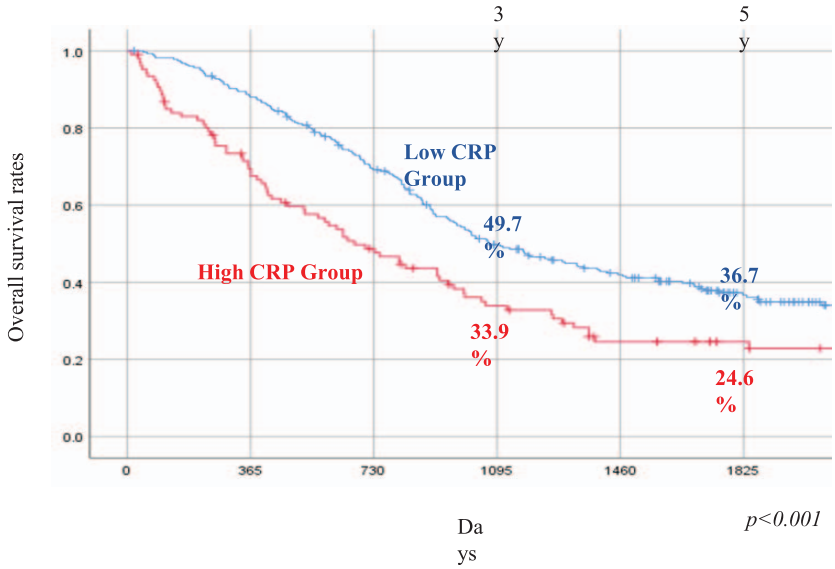

Fig. 1 Kaplan-Meier survival curve

survival between the 2 groups in patients with an R0 resection (Fig. 2).

We also examined only those patients who underwent palliative surgery. A total of 262 patients were unable to undergo R0 surgical resection in this series. Similar to the results of the overall stage IV study, many cases existed in HCG that showed a high CEA level within the patient background. Differences did not exist concerning age, sex, ASA–PS, BMI, and other variables listed in Table 6. In postoperative short-term results, as shown in Table 7, postoperative chemotherapy was introduced to 67.4% of patients in HCG and 83.8% of patients in LCG ($P = 0.002$). Comparing overall survival rates, HCG had significantly lower survival rates than LCG (Fig. 3). Multivariate analysis showed that CRP values above 1.0 mg/dL, poorly differentiated histopathology, and the absence of chemotherapy were risk factors affecting overall survival (Table 8).

Table 3 Multivariate analysis of factors affecting survival rates

	HR	95.0% CI	*P* value
Sex	0.938	0.71–1.24	0.653
Age	1.009	0.996–1.022	0.195
Double cancers	0.96	0.591–1.56	0.868
Multiple cancers	1.121	0.685–1.833	0.650
Clavien-Dindo Grade II or higher	1.075	0.758–1.525	0.684
CEA ≥5.0 ng/mL	0.828	0.607–1.13	0.234
CRP ≥1.0 mg/dL	0.718	0.54–0.954	0.022
Histologic type	0.458	0.314–0.667	<0.001
Lymphatic invasion	0.818	0.62–1.081	0.158
Vein invasion	0.602	0.389–0.931	0.023
Tumor depth	0.804	0.609–1.061	0.124
Lymph node metastasis	1.003	0.701–1.436	0.986
With peritoneal dissemination	0.817	0.592–1.128	0.219
R0 surgical resection	0.19	0.132–0.274	<0.001

Discussion

CRP is an acute-phase protein that is synthesized and secreted by the liver and is recognized as part of the inflammatory response.[15] CRP is useful for

Table 4 Clinical characteristics in patients with R0 surgical resection

	High CRP group	Low CRP group	*P* value
n	18	104	
Sex, n (%)			
Male	12 (66.7)	58 (55.8)	
Female	6 (33.3)	46 (44.2)	0.388
Age, y	63.22 ± 9.45	64.71 ± 10.66	0.400
Double cancers, n (%)			
Yes	1 (5.6)	7 (6.7)	
No	17 (94.4)	97 (93.3)	0.665
Multiple cancers, n (%)			
Yes	1 (5.6)	7 (6.7)	
No	17 (94.4)	97 (93.3)	0.665
ASA–PS, n (%)			
1	9 (50.0)	39 (37.5)	
2	6 (33.3)	57 (54.8)	
3	3 (16.7)	8 (7.7)	0.187
Previous abdominal surgery, n (%)			
Yes	6 (33.3)	41 (39.4)	
No	12 (66.7)	63 (60.6)	0.624
CEA value 5.0 ng/mL, n (%)			
≥5.0 ng/mL	14 (77.8)	66 (63.5)	
<5.0 ng/mL	4 (22.2)	38 (36.5)	0.238
BMI, kg/m^2	21.41 ± 3.43	22.49 ± 3.29	0.297

Table 5 Short-term outcomes in patients with R0 surgical resection

	High CRP group	Low CRP group	*P* value
n	18	104	
Laparoscopic surgery, n (%)			
Yes	7 (38.9)	67 (64.4)	
No	11 (61.1)	37 (35.6)	0.041
Operation time, min	251.28 ± 124.55	228.74 ± 97.67	0.593
Blood loss, mL	357.78 ± 441.31	193.64 ± 358.31	0.032
Postoperative complication			
Clavien–Dindo Grade ≥II, n (%)			
Yes	2 (11.1)	13 (12.5)	
No	16 (88.9)	91 (87.5)	0.614
Urination disorder (self-catheterization), n (%)			
Yes	0 (0.0)	2 (1.9)	
No	18 (100.0)	102 (98.1)	0.726
Postoperative hospital stay, days	10.33 ± 5.27	9.93 ± 6.47	0.575
Histopathology, n (%)			
Well, moderate	15 (83.3)	96 (92.3)	
Poor, mucinous	3 (16.7)	8 (7.7)	0.207
Lymphatic invasion, n (%)			
Positive	13 (72.2)	54 (51.9)	
Negative	5 (27.8)	50 (48.1)	0.119
Venous invasion, n (%)			
Positive	15 (83.3)	85 (81.7)	
Negative	3 (16.7)	19 (18.3)	0.619
Tumor depth, n (%)			
T1–3	11 (61.1)	74 (71.2)	
T4	7 (38.9)	30 (28.8)	0.392
Lymph node metastasis, n (%)			
Positive	13 (72.2)	77 (74.0)	
Negative	5 (27.8)	27 (26.0)	0.512
Peritoneal dissemination, n (%)			
Positive	2 (11.1)	16 (15.4)	
Negative	16 (88.9)	88 (84.6)	0.481

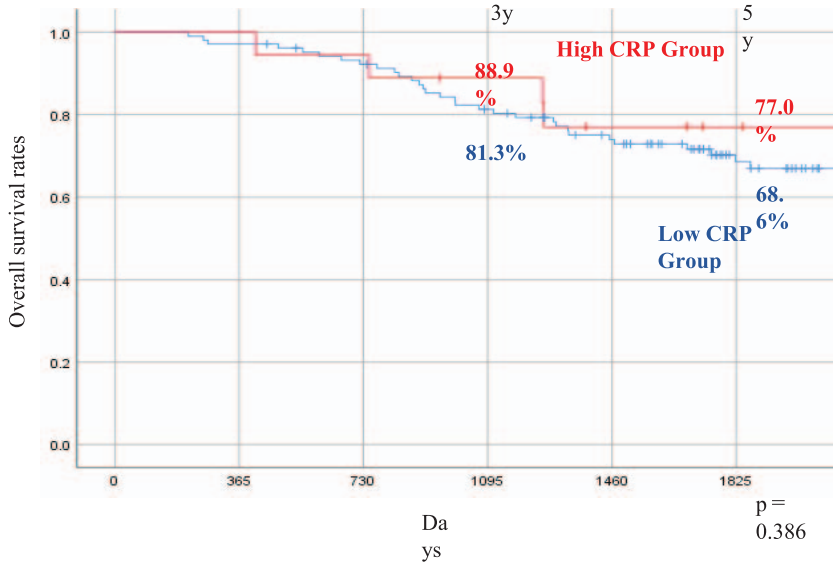

Fig. 2 Kaplan-Meier survival curve in patients with R0 surgical resection

Table 6 Clinical characteristics in patients without R0 surgical resection

	High CRP group	Low CRP group	*P* value
n	89	173	
Sex, n (%)			
Male	61 (68.5)	114 (65.9)	
Female	28 (31.5)	59 (34.1)	0.667
Age, y	68.09 ± 10.17	65.80 ± 11.29	0.105
Double cancers, n (%)			
Yes	7 (7.9)	15 (8.7)	
No	82 (92.1)	158 (91.3)	0.824
Multiple cancers, n (%)			
Yes	8 (9.0)	12 (6.9)	
No	81 (91.0)	161 (93.1)	0.554
ASA–PS, n (%)			
1	32 (36.0)	64 (37.4)	
2	45 (50.6)	90 (52.6)	
3	12 (13.5)	17 (9.9)	0.690
Previous abdominal surgery, n (%)			
Yes	28 (31.5)	60 (34.7)	
No	61 (68.5)	113 (65.3)	0.601
CEA value 5.0 ng/mL, n (%)			
≥5.0 ng/mL	77 (86.5)	131 (75.7)	
<5.0 ng/mL	12 (13.5)	42 (24.3)	0.041
BMI, kg/m^2	22.37 ± 3.91	22.58 ± 3.71	0.685

ASA-PS, American Society of Anesthesiologists physical status; CEA, Carcinoembryonic antigen; BMI, Body mass index; CRP, C-reactive protein.

predicting complications after the intestinal resection of malignant tumors and in the prognosis of patients who have undergone surgical resection of malignant tumors.[7–9,16–19] Increased CRP is observed in many conditions such as infection, inflammation, malignant tumors, and trauma; previous studies have suggested a link between inflammation and cancer. In addition to CRP, other indicators of inflammation include the Glasgow prognostic score, calculated from CRP and albumin, the neutrophil-to-lymphocyte ratio, interleukin-6, matrix metalloproteinase-9, and other variables; their relationship with the degree of malignant tumor progression and prognosis has been described.[20,21] Other studies have demonstrated that the CEA value correlates with the prognosis of colorectal cancer.[22,23] In the present study, patients in HCG with palliative surgery showed a significantly high CEA. However, HCG patients who underwent an R0 surgical resection did not show a significantly high CEA, and CEA was not found to be a prognostic factor in our study.

In short-term outcomes, univariate analysis revealed that a small number of people could perform an R0 surgical resection with HCG. In stage IV colorectal cancer, the ability to perform R0 surgery is also a prognostic factor.[24] Few cases exist in which an R0 surgical resection is possible in HCG, resulting in a poor prognosis. In addition to the high CRP value in multivariate analysis, the inability to perform an R0 surgical resection was also a factor that reduced the survival rate.

In this study, HCG patients with palliative surgery showed a significantly lower chemotherapy induction rate. Prechemotherapy CRP levels help predict prognosis in patients with colorectal cancer receiving oxaliplatin-based chemotherapy.

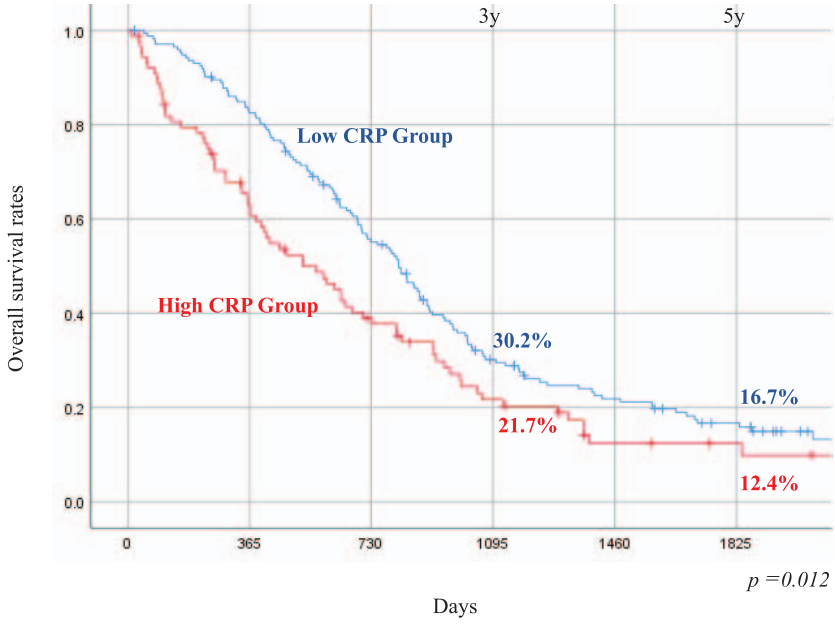

Fig. 3 Kaplan–survival curve in patients without R0 surgical resection

Table 7 Short-term outcomes in patients without R0 surgical resection

	High CRP group	Low CRP group	*P* value
n	89	173	
Laparoscopic surgery, n (%)			
Yes	55 (61.8)	122 (70.5)	
No	34 (38.2)	51 (29.5)	0.153
Operation time, min	209.00 ± 80.67	228.98 ± 77.74	0.017
Blood loss, mL	164.13 ± 298.83	116.88 ± 219.96	0.454
Postoperative complication			
Clavien-Dindo Grade ≥II, n (%)			
Yes	17 (19.1)	29 (16.8)	
No	72 (80.9)	144 (83.2)	0.638
Urination disorder (self-catheterization), n (%)			
Yes	3 (3.4)	4 (2.3)	
No	86 (96.6)	169 (97.7)	0.444
Postoperative hospital stay, days	11.49 ± 10.35	11.57 ± 16.36	0.939
Histopathology, n (%)			
Well, moderate	77 (86.5)	151 (87.3)	
Poor, mucinous	12 (13.5)	22 (12.7)	0.861
Lymphatic invasion, n (%)			
Positive	49 (55.1)	105 (60.7)	
Negative	40 (44.9)	68 (39.3)	0.380
Venous invasion, n (%)			
Positive	75 (84.3)	159 (91.9)	
Negative	14 (15.7)	14 (8.1)	0.058
Tumor depth, n (%)			
T1–T3	53 (59.6)	111 (64.2)	
T4	36 (40.4)	62 (35.8)	0.465
Lymph node metastasis, n (%)			0.283
Positive	69 (78.4)	145 (83.8)	
Negative	20 (22.5)	28 (16.2)	0.283
Peritoneal dissemination, n (%)			
Positive	24 (27.0)	37 (21.4)	
Negative	65 (73.0)	136 (78.6)	0.312
Chemotherapy, n (%)			
Yes	60 (67.4)	145 (83.8)	
No	29 (32.6)	28 (16.2)	0.002

Table 8 Multivariate analysis of factors affecting survival rate in patients without R0 surgical resection

	HR	95.0% CI	*P* value
Sex	1.122	0.827–1.521	0.459
Age	1.004	0.990–1.017	0.604
Double cancers	1.158	0.670–2.002	0.599
Multiple cancers	1.552	0.884–2.726	0.126
Clavien-Dindo Grade ≥II	1.025	0.704–1.494	0.896
CEA value ≥5.0 ng/mL	0.777	0.544–1.110	0.166
CRP ≥1.0 mg/dL	0.724	0.531–0.986	0.041
Histologic type	0.500	0.327–0.764	0.001
Lymphatic invasion	0.912	0.673–1.236	0.553
Venous invasion	0.703	0.422–1.171	0.176
Tumor depth	0.846	0.623–1.149	0.285
Lymph node metastasis	0.717	0.472–1.089	0.118
Peritoneal dissemination	0.792	0.554–1.133	0.202
Chemotherapy	3.685	2.517–5.396	<0.001

Chemotherapy is the most important treatment for unresectable colorectal cancer, suggesting that the low induction rate of chemotherapy in HCG may contribute to the decrease in survival rate observed.

Our results indicate that preoperative CRP levels were not useful for a subsequent prognosis in patients with an R0 surgical resection. Therefore, it is important to aim for an R0 surgical resection, regardless of the CRP level, if possible. If curative surgical resection cannot be performed in patients with high preoperative CRP levels and a poor prognosis, it is important to consider treatment strategies. CRP levels before treatment may be a useful biomarker for prudent decision-making if difficulty exists in performing an R0 surgical resection in patients with stage IV colorectal cancer.

Conclusion

These results suggest that the preoperative CRP level may be a useful biomarker for the prognosis of incurable stage IV colorectal cancer.

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