

Elevated Postoperative Levels of Serum C-reactive Protein Are Associated With Shorter Long-term Survival After Resection of Colorectal Liver Metastases, Regardless of the Occurrence of Infectious Complications

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Abstract. *Background/Aim:* Recently, elevated levels of postoperative inflammatory markers have been reported to be associated with poorer long-term survival outcomes, regardless of the occurrence of infectious complications, in gastroenterological malignancies. The aim of this study was to evaluate the association between postoperative inflammation and shorter long-term survival after resection of colorectal liver metastases. *Patients and Methods:* A total of 104 patients who underwent R0 resection for colorectal liver metastases were enrolled. The CRP_{max} levels were defined as the highest postoperative serum C-reactive protein levels during hospital stay. *Results:* The high-CRP_{max} group had a significantly lower relapse-free survival rate than the low-CRP_{max} group, regardless of the occurrence of infectious complications. *Conclusion:* In colorectal liver metastasis as well as other malignancies, elevated postoperative levels of serum C-reactive protein are associated with shorter long-term survival, regardless of the occurrence of infectious complications.

In colorectal cancer, the liver is the most common site for synchronous distant metastasis and recurrence after curative surgery (1-3). Surgical resection is the only potentially

curative therapeutic option and is accepted as the optimal treatment for colorectal liver metastases, providing 5-year survival rates of 37%-58% after complete resection (4-8). However, the incidence of postoperative complications, such as liver failure, bile leakage and intraabdominal abscess, remains high (9-12), although advances in surgical techniques and perioperative management contribute to decreased morbidity rates. Postoperative infectious complications have been reported to be associated with shorter long-term survival of patients with colorectal liver metastasis (13-16). This is because the increased production of inflammatory cytokines caused by infectious complications provides a favorable environment for the growth of micrometastases (17-21).

Recently, postoperative severe inflammation caused by excessive surgical stress as well as that induced by the postoperative infectious complications has been reported to be associated with shorter long-term survival in patients who undergo curative resection of the primary tumor in cases of gastroenterological malignancies, including gastric cancer and colorectal cancer (22, 23).

The present study evaluated whether or not elevated postoperative levels of serum C-reactive protein are associated with shorter long-term survival after resection of colorectal liver metastases, regardless of the occurrence of infectious complications.

Patients and Methods

Patients. A total of 104 patients who underwent R0 resection for colorectal liver metastases at Osaka City University Hospital between January 2001 and December 2017 were enrolled in this

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study. R0 resection was defined as no microscopic evidence of the tumor at or within 1 mm of the margin. Two cases of simultaneous multiple primary cancer were excluded from this study.

This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Methods. Blood samples were taken for routine laboratory analysis of serum CRP levels at postoperative day (POD) 1, 3 and 7. In addition, blood tests were added or changed as needed according to the decision of the attending physician. The CRP_{max} levels were defined as the highest postoperative serum CRP levels during the hospital stay. An appropriate cut-off value of the CRP_{max} levels was determined according to a receiver operating characteristic (ROC) curve analysis. The patients were then classified into the low-CRP_{max} group and the high-CRP_{max} group, and the relationship between the CRP_{max} levels and the relapse-free survival was assessed.

Postoperative infectious complications include both surgical site infection and remote infection. Because patients without postoperative infectious complications were the main subjects in this study, the severity of the complications, such as Clavien-Dindo classification, was not evaluated.

Furthermore, we conducted a subgroup analysis limited to patients without postoperative infectious complications in order to evaluate the prognostic significance of the CRP_{max} levels independently of the presence or absence of postoperative infectious complications and to investigate the causes of an increased CRP_{max} levels other than infectious complications.

Statistical analyses. The relapse-free survival was defined as the interval between the date of operation and the date of the diagnosis of the first recurrence, death from any cause or last follow-up. The significance of differences in the CRP_{max} levels and the clinicopathological factors were analyzed using a chi-squared test, Fisher's exact test and Mann-Whitney's *U*-test. Survival curves were estimated using the Kaplan-Meier method, and the differences in the survival curves were assessed with the log-rank test. *p*-Values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics. As shown in Table I, the study cohort included 55 male and 49 female patients, with a median age of 65.5 years old. Fifty-two patients had synchronous colorectal liver metastasis, and 52 had metachronous colorectal liver metastasis. Fifty-four patients had a single colorectal liver metastasis, and 50 had multiple colorectal liver metastases. The median diameter of the colorectal liver metastasis was 2.85 cm. The median amount of bleeding was 335 ml. The median operation time was 280.5 min. Thirteen (12.5%) patients developed postoperative infectious complications, including 18 surgical site infections and 3 remote infections (some had ≥2 infectious complications). The median duration of follow-up was 55.8 months.

Table I. Patient characteristics.

Age (years)	
Median (range)	65.5 (22-87)
Gender, n	
Male	55
Female	49
Detection of liver metastases, n	
Synchronous	52
Metachronous	52
Size of largest liver metastases	
Median (range)	2.85 (0.4-13.0)
Number of liver metastases, n	
1	54
≥2	50
Location of primary tumor, n	
Right side	30
Left side	74
Histological type of primary tumor, n	
Well-/moderately differentiated	98
Poorly differentiated/Mucinous	3
Unknown	3
Depth of primary tumor, n	
T1-3	67
T4	35
Unknown	2
Lymph node metastasis of primary tumor, n	
Negative	41
Positive	61
Unknown	2
Serum CEA level (ng/ml), n	
≤5.0	23
>5.0	80
Unknown	1
The amount of bleeding (ml)	
Median (range)	335.0 (3-2225)
Operation time (min)	
Median (range)	280.5 (97-609)
Postoperative infectious complications, n*	
Surgical site infection	18
Remote infection	3
None	91

*Some patients had two or more infectious complications. CEA: Carcinoembryonic antigen.

Seventy-two patients relapsed, and 50 patients died during the follow-up period. Patients who died within 30 days following hepatic resection were not included in this study.

Classification and survival analysis according to CRP_{max} levels in all patients enrolled in this study. We used the CRP_{max} levels, which were a continuous variable, as the test variable and recurrence as the state variable. According to the ROC curve analysis of the CRP_{max} levels, 7.13 was adopted as the cut-off value (sensitivity: 72.6%, specificity: 54.8%) (Figure 1), and the patients were classified into the low-CRP_{max} group (n=37) and the high-CRP_{max} group (n=67) based on this value. The high-CRP_{max} group had a significantly lower relapse-free

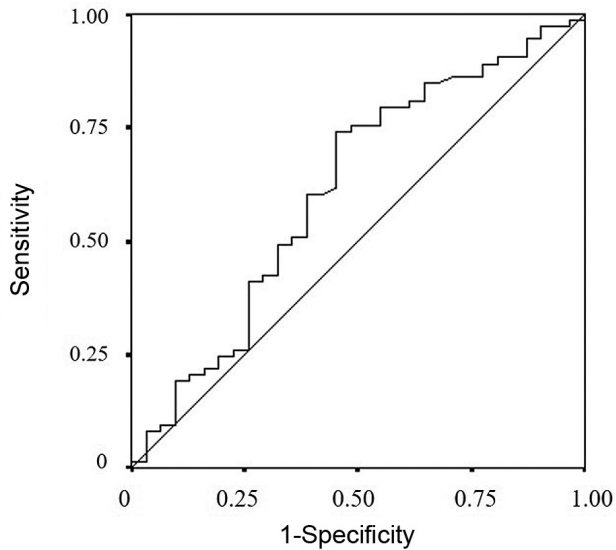


Figure 1. A receiver operating characteristic curve analysis of CRP_{max} levels. Area under the curve=0.613; 95% Confidence Interval=0.490-0.737; $p=0.068$.

survival rate than the low- CRP_{max} group ($p=0.0412$) (Figure 2). Thirteen (12.5%) patients developed postoperative infectious complications. The median CRP_{max} levels of the patients with postoperative infectious complications were significantly higher than those of the patients without infectious complications (14.60 vs. 7.92) ($p=0.001$).

Subgroup analyses limited to patients without postoperative infectious complications. Similarly, in a subgroup analysis limited to the patients without postoperative infectious complications, the high- CRP_{max} group had a significantly lower relapse-free survival rate than the low- CRP_{max} group ($p=0.0372$) (Figure 3).

The risk factors of elevated CRP_{max} levels after resection of colorectal liver metastasis were examined (Table II). Only large amount of bleeding (≥ 350 ml) was associated with a high CRP_{max} level ($p=0.033$).

Discussion

In this study, elevated postoperative levels of serum C-reactive protein were shown to be associated with shorter long-term survival after resection of colorectal liver metastases, regardless of the occurrence of infectious complications.

Infectious complications increase the levels of inflammatory cytokines, such as interleukin-6 (IL-6), and subsequent immunosuppression promotes the proliferation of occult micrometastases (19-21). This phenomenon is also caused by excessive surgical stress, even in patients without postoperative

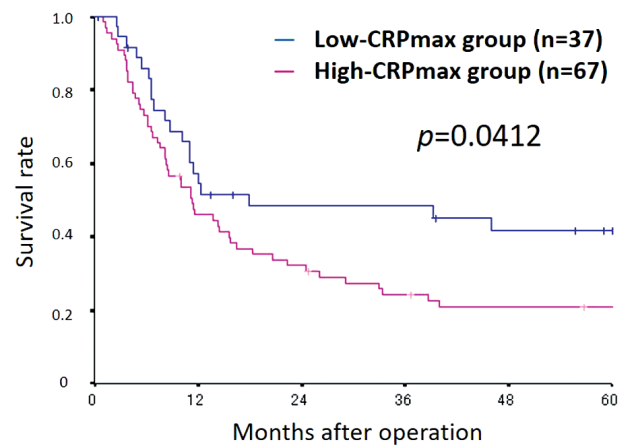


Figure 2. Kaplan-Meier survival curve for the relapse-free survival according to the CRP_{max} levels. High CRP_{max} levels were associated with shorter relapse-free survival ($p=0.0412$).

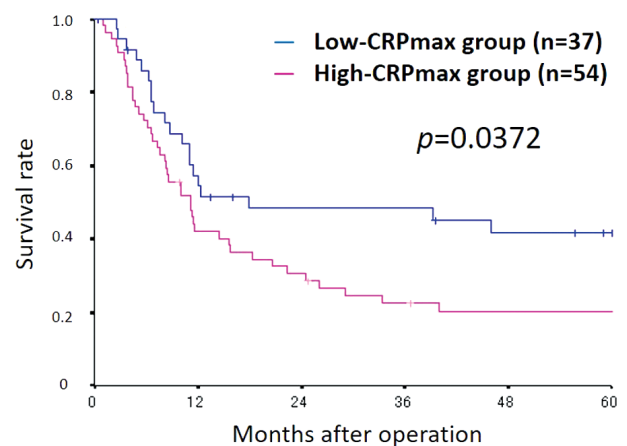


Figure 3. Kaplan-Meier survival curve for relapse-free survival according to the CRP_{max} levels in patients without postoperative infectious complications. High CRP_{max} levels were associated with shorter relapse-free survival ($p=0.0372$).

infectious complications. Postoperative infectious complications have been found to be associated with a worse prognosis of patients with various cancers (16, 24-26). However, the severity of complications has been relatively rarely considered, and even when it has been considered, only simple classification using the Clavien-Dindo classification system was performed (13-15). Furthermore, the types of complications have been rarely considered, although it has been reported that some types of infectious complications do not affect the prognosis (16). Therefore, the presence or absence of infectious complications alone is not sufficient for use as a predictor of the prognosis.

Table II. Correlations between CRP_{max} levels and clinicopathological factors in patients without postoperative infectious complications.

Factors	CRP _{max}		p-Value
	Low (n=37)	High (n=54)	
Gender, n			
Male	15	30	
Female	22	24	0.202
Age (years), n			
<75	31	46	
≥75	6	8	>0.999
Detection of liver metastasis, n			
Synchronous	14	29	
Metachronous	23	25	0.199
Size of largest liver metastases (cm), n			
<5	32	42	
≥5	5	12	0.413
Number of liver metastases, n			
1	21	27	
≥2	16	27	0.669
Location of primary tumor, n			
Right side	10	14	
Left side	27	40	>0.999
Histological type of primary tumor, n			
Well-/moderately differentiated	36	50	
Poorly differentiated/Mucinous	0	2	0.511
Unknown	1	2	
Depth of primary tumor, n			
T1-3	24	35	
T4	13	17	0.824
Unknown	0	2	
Lymph node metastasis o primary tumor, n			
Negative	18	17	
Positive	19	35	0.186
Unknown	0	2	
Serum CEA level (ng/ml), n			
≤5	9	11	
>5	28	42	0.798
Unknown	0	1	
The amount of bleeding (ml), n			
<350	24	22	
≥350	13	32	0.033
Operation time (min), n			
<180	10	8	
≥180	27	46	0.185
Transfusion, n			
Negative	30	43	
Positive	7	11	>0.999

CRP: C-reactive protein; CEA: carcinoembryonic antigen.

The serum CRP level is a comprehensive indicator that includes the degree of postoperative inflammation. In a recent report on the prognostic significance of postoperative serum CRP levels in patients with gastric cancer (22), it was concluded that postoperative CRP elevation was a better

predictor than the occurrence of infectious complications. In the present study, elevated CRP_{max} levels were found to be associated with shorter long-term survival, independently of the presence or absence of postoperative complications in patients with colorectal liver metastasis. Therefore, strong postoperative inflammation adversely affects long-term survival regardless of the cause of inflammation.

Although it is widely recognized that an increase in intraoperative blood loss causes immunosuppression and subsequent deterioration of prognosis (27), the mechanism by which the amount of bleeding is associated with the CRP_{max} levels is unclear. A large amount of bleeding may indirectly indicate a surgical procedure with major invasion or bleeding itself may be the cause of increased inflammation.

Adjuvant chemotherapy after curative resection of colorectal liver metastases has been reported to be effective for treating patients with a high risk of recurrence (23, 28, 29). Therefore, risk classification based on CRP_{max} levels may help identify patients who are likely to benefit from adjuvant chemotherapy after curative resection of colorectal liver metastases.

To reduce postoperative inflammation, the following were important: (i) selection of a minimally invasive procedure, (ii) reduction of the amount of bleeding, (iii) reduction of postoperative infectious complications and (iv) appropriate response to complications.

Several limitations associated with the present study should be mentioned. First, the current study was a retrospective study of a small cohort in a single center. Second, although the serum CRP levels were routinely measured at POD 1, 3 and 7, the measurement of serum CRP levels was added or changed as needed according to the decision of the attending physician. Therefore, the days of blood tests were not always fixed. Third, we did not assess the overall survival in this study. This study included some patients who underwent resection of colorectal liver metastases 20 years ago. With the development of new cytotoxic and molecular-targeted therapies, the survival after recurrence has been significantly improved compared with 20 years ago. Therefore, we assessed only the relapse-free survival.

Conclusion

Elevated postoperative levels of serum C-reactive protein were revealed to be associated with shorter long-term survival after resection of colorectal liver metastases, regardless of the occurrence of infectious complications. Surgeons should minimize postoperative inflammation by reducing excessive surgical stress as well as performing strict postoperative management and reducing postoperative complications.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

MS designed the study, performed the statistical analysis and drafted the manuscript. KK, WE and YO collected the clinical data and revised the manuscript critically. SK, KM, KH and MO designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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