

# Postoperative Level of C-Reactive Protein Is a Prognosticator After Esophageal Cancer Surgery With Perioperative Steroid Therapy and Enhanced Recovery After Surgery Care

KAZUKI KANO<sup>1,2\*</sup>, TORU AOYAMA<sup>2\*</sup>, YUKIO MAEZAWA<sup>2</sup>, TSUTOMU HAYASHI<sup>1,2</sup>, TAKANOBU YAMADA<sup>1,2</sup>, HIROSHI TAMAGAWA<sup>2</sup>, TSUTOMU SATO<sup>2</sup>, HARUHIKO CHO<sup>2</sup>, TAKAKI YOSHIKAWA<sup>2</sup>, YASUSHI RINO<sup>2</sup>, MUNETAKA MASUDA<sup>2</sup>, TAKASHI OSHIMA<sup>1</sup> and TAKASHI OGATA<sup>1</sup>

<sup>1</sup>Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan;

<sup>2</sup>Department of Surgery, Yokohama City University, Kanagawa, Japan

**Abstract.** *Background:* This study investigated the impact of postoperative C-reactive protein (CRP) level on survival in patients with esophageal cancer who received perioperative steroid therapy and enhanced recovery after surgery (ERAS) care. *Patients and Methods:* Overall, 115 patients were retrospectively reviewed. The patients were classified into those with a high CRP level ( $\geq 4.0$  mg/dl) on postoperative day 4 and those with low CRP level ( $< 4.0$  mg/dl). The risk factors for overall survival (OS) and recurrence-free survival (RFS) were identified. *Results:* The OS and RFS rates at 5 years after surgery were significantly low in patients with high CRP level on postoperative day 4. The multivariate analysis demonstrated that high CRP level on postoperative day 4 was a significant independent risk factor for OS and RFS. *Conclusion:* The present results suggest that the postoperative CRP level can be a prognosticator in patients with esophageal cancer who have received perioperative steroid therapy and ERAS care.

Esophageal cancer is the world's eighth most-common cancer and the sixth leading cause of cancer-related death among those with cancer (1). Multimodal therapy, including curative resection and perioperative adjuvant treatment, is

essential to a cure for esophageal cancer (2-8). However, patients with esophageal cancer often have tumor recurrence, even after curative treatment (9). Therefore, it is important to identify prognostic factors for patients with esophageal cancer in order to select candidates for more aggressive treatment and thereby improve survival.

Various clinicopathological factors, including weight loss, lymph node metastasis, and postoperative infectious complications, have been reported to be significant prognostic factors that can be used to predict survival in patients with esophageal cancer (10-12). Recently, systemic inflammatory responses after surgery have been reported to be associated with survival in patients with cancer (13, 14). C-Reactive protein (CRP) is regarded as a biochemical marker of a systemic inflammatory response (15). In addition, a postoperatively elevated CRP level is associated with poor outcomes in various malignancies, including esophageal cancer (15-18).

Modified procedures for perioperative surgical care, such as steroid therapy and enhanced recovery after surgery (ERAS) care, have been introduced to esophageal cancer surgery. These perioperative surgical care procedures have been reported to reduce systemic inflammatory responses, including postoperative serum CRP level (19-22). However, the clinical impact of postoperative serum CRP level on the survival of patients with esophageal cancer who receive modified perioperative surgical care remains unclear.

The aim of this study was to assess whether the postoperative serum CRP level has a clinical impact on survival in patients with esophageal cancer who receive curative treatment and modified perioperative surgical care.

## Patients and Methods

*Patient data.* Between January 2011 and September 2015, the medical records of consecutive patients who underwent esophagectomy for esophageal cancer at our Department were reviewed, and patients who met the following conditions were studied: (i) A histologically proven

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\*These Authors contributed equally to this study.

*Correspondence to:* Takashi Oshima and Takashi Ogata, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2-3-2, Nakao, Asahi-ku, Yokohama, Kanagawa 241-8515, Japan. Tel: +81 455202222, Fax: +81 455202202, e-mail: oshimat@kcch.jp and ogatat@kcch.jp

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diagnosis of primary esophageal squamous cell carcinoma located in the thoracic esophagus, (ii) clinical stage IB to stage III (excluding T4) disease as evaluated according to the Seventh Edition of the Tumor-node-metastasis Classification established by the Union for International Cancer Control (UICC) (23), and (iii) treatment by neoadjuvant chemotherapy followed by complete resection of the esophageal cancer with radical lymph node dissection. The exclusion criteria were as follows: (i) patients who underwent R2 or R1 resection, and (ii) patients who received postoperative chemotherapy.

**Neoadjuvant chemotherapy.** Cisplatin plus 5-fluorouracil was given twice at an interval of 4 weeks. A dose of 80 mg/m<sup>2</sup> cisplatin was given as an intravenous drip infusion on day 1; 5-fluorouracil was administered in a dose of 800 mg/m<sup>2</sup> as a continuous infusion on days 1-5 (4).

**Surgical procedure.** Surgical resection was generally performed 4-6 weeks after the completion of chemotherapy. Our standard procedures consisted of open subtotal esophagectomy *via* right thoracotomy, reconstruction with a gastric tube through the posterior mediastinal route or retrosternal route, and anastomosis in the cervical incision. In principle, two-field lymph node dissection was indicated when tumors were located at the middle thoracic to lower thoracic esophagus, while three-field was applied for upper thoracic tumors. Multiple drains were placed; one to the posterior side of the thoracic cavity and the others on either side of the neck, which were usually removed on postoperative day (POD) 7. A feeding tube was routinely placed at the stomach or duodenum. The patients did not have a nasal-gastric tube.

**Perioperative care.** All of the patients received uniform perioperative management based on the ERAS program, which included antibiotic prophylaxis and steroid therapy. Cefazolin (1 g) was administered 30 min before the surgical incision, every 3 hours during surgery, and at a dose of 2 g on POD 1. Methylprednisolone was administered at a dose of 500 mg on the day of surgery, 250 mg on POD 1, and 125 mg on POD 2 (20, 21). Our ERAS program satisfied the 15 conditions proposed by Fearon *et al.* (24). Briefly, the patients were allowed to eat 30% rice porridge until midnight the day before the surgery and were required to drink two 500-ml plastic bottles containing oral rehydration solution by 3 h before surgery. Enteral nutrition was started on POD 1. Oral intake was initiated on POD 6, beginning with water and gelatinous foods. The patients began to eat solid food on POD 9, starting with rice gruel and soft food and progressing in three steps to regular food intake.

**Definition of surgical complications and measurement of CRP.** All data were retrospectively retrieved from the patients' records. Postoperative infectious complications were defined as grade III or higher complications associated with anastomotic leakage, pneumonia, abdominal abscess, surgical site infection, or pyothorax according to the Clavien–Dindo classification (25), occurring during hospitalization within 30 days after surgery. These complications were assessed on the basis of the clinical symptoms, blood tests, and X-ray imaging on POD 1, 2, 4, 6, 8, and subsequently. If infectious complications were suspected, precise examinations, such as computed tomography and esophagography, were performed. Based on a previous study (26), the patients were classified into those with high CRP levels ( $\geq 4.0$  mg/dl) on POD 4 and those with low CRP levels ( $< 4.0$  mg/dl) on POD 4.

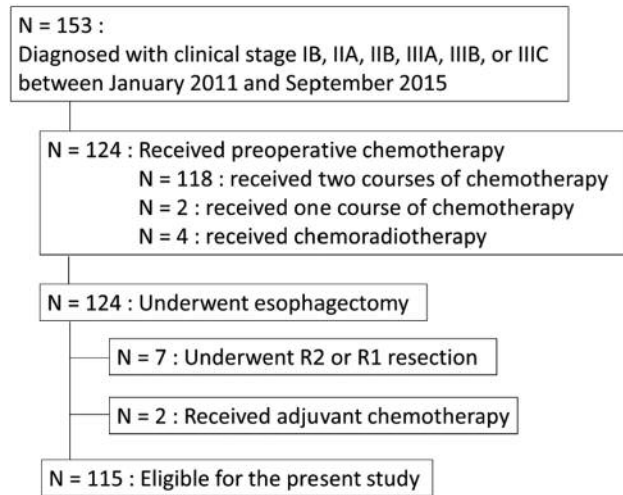


Figure 1. Flow diagram of the 153 patients who were given a diagnosis of clinical stage IB, IIA, IIB, IIIA, IIIB, or IIIC esophageal cancer between January 2011 and September 2015.

**Follow-up.** The patients were followed-up at an outpatient clinic. The follow-up program of postoperative surveillance principally consisted of a physical examination, blood chemical analysis including tumor markers every 3 months for the first year and every 6 months thereafter. Computed tomography of the neck, chest, and abdomen was performed every 6 months. Disease recurrence was diagnosed by computed tomography. Equivocal mass was checked by fluorodeoxyglucose positron-emission tomography.

**Evaluations and statistical analyses.** Overall survival (OS) was defined as the period between the date of surgery and death. Recurrence-free survival (RFS) was defined as the period between the date of surgery and recurrence or death, whichever came first. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. A Cox proportional hazards model was used to perform univariate and multivariate survival analyses to identify prognosticators. An unpaired Student's *t*-test or chi-square test was used to compare the two groups. *p*-Values of less than 0.05 were considered to indicate statistical significance. The survival data were obtained from the hospital records or from the city registry system. All of the statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Australia). More precisely, it is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics (27).

**Ethics.** The present study was conducted in compliance with the 'Ethical Guidelines for Clinical Research' and with the Helsinki Declaration of 1975, as revised in 1983. This study was approved by the Institutional Review Board (IRB) of our department (2018.epidemiologic study-72). Written informed consent for using clinical data without identifying personal information was obtained from all patients before surgery.

Table I. Comparison of clinicopathological factors between the patients with high C-reactive protein (CRP) and those with low CRP on postoperative day 4.

Variable	All patients (n=115)	High CRP group (n=40)	Low CRP group (n=75)	p-Value
Age, years				
Median (range)	66 (48-77)	66 (57-77)	67 (48-77)	0.941
Gender				
Male	92 (80.0%)	35 (87.5%)	57 (76.0%)	0.220
Female	23 (20.0%)	5 (12.5%)	18 (24.0%)	
Preoperative serum albumin, g/dl				
Median (range)	4.1 (2.3-6.4)	4.1 (3.1-4.8)	4.1 (2.3-6.4)	0.965
ASA-PS				
1	17 (14.8%)	7 (17.5%)	10 (13.3%)	0.752
2	97 (84.3%)	33 (82.5%)	64 (85.3%)	
3	1 (0.9%)	0 (0.0%)	1 (1.3%)	
Main tumor location				
Upper thoracic esophagus	16 (13.9%)	6 (15.0%)	10 (13.3%)	0.795
Middle thoracic esophagus	60 (52.2%)	19 (47.5%)	41 (54.7%)	
Lower thoracic esophagus	39 (33.9%)	15 (37.5%)	24 (32.0%)	
Lymph node dissection				
Two-field	93 (80.9%)	33 (82.5%)	60 (80.0%)	0.808
Three-field	22 (19.1%)	7 (17.5%)	15 (20.0%)	
Operative time, min				
Median (range)	400 (298-593)	430 (343-593)	381 (298-593)	0.006
Intraoperative blood loss, ml				
Median (range)	420 (110-3000)	515 (180-3000)	365 (110-2350)	0.004
Postoperative infectious complications <sup>a</sup>				
<Grade 3	95 (82.6%)	24 (60.0%)	71 (94.7%)	<0.001
≥Grade 3	20 (17.4%)	16 (40.0%)	4 (5.3%)	
Pathological T factor <sup>b</sup>				
T0	7 (6.1%)	0 (0.0%)	7 (9.3%)	0.103
T1a	6 (5.2%)	3 (7.5%)	3 (4.0%)	
T1b	20 (17.4%)	5 (12.5%)	15 (20.0%)	
T2	18 (15.7%)	7 (17.5%)	11 (14.7%)	
T3	57 (49.6%)	20 (50.0%)	37 (49.3%)	
T4a	1 (0.9%)	1 (2.5%)	0 (0.0%)	
T4b	6 (5.2%)	4 (10.0%)	2 (2.7%)	
Pathological N factor <sup>b</sup>				
N0	42 (36.5%)	17 (42.5%)	25 (33.3%)	0.742
N1	38 (33.0%)	11 (27.5%)	27 (36.0%)	
N2	27 (23.5%)	9 (22.5%)	18 (24.0%)	
N3	8 (7.0%)	3 (7.5%)	5 (6.7%)	
Pathological stage <sup>b</sup>				
0	4 (3.5%)	0 (0.0%)	4 (5.3%)	0.399
IA	8 (7.0%)	2 (5.0%)	6 (8.0%)	
IB	9 (7.8%)	4 (10.0%)	5 (6.7%)	
IIA	19 (16.5%)	9 (22.5%)	10 (13.3%)	
IIB	16 (13.9%)	4 (10.0%)	12 (16.0%)	
IIIA	32 (27.8%)	9 (22.5%)	23 (30.7%)	
IIIB	12 (10.4%)	4 (10.0%)	8 (10.7%)	
IIIC	15 (13.0%)	8 (20.0%)	7 (9.3%)	

ASA-PS: American Society of Anesthesiologists Physical Status. <sup>a</sup>According to Clavien–Dindo classification (25). <sup>b</sup>According to the Union for International Cancer Control (23).

## Results

**Patient characteristics.** A total of 153 patients were given a diagnosis of esophageal squamous cell carcinoma of clinical stage IB, IIA, IIB, IIIA, IIIB, or IIIC between January 2011

and September 2015. A flow diagram of the 153 patients is shown in Figure 1. One hundred and fifteen of these patients were eligible for the present study (75.2%). Forty patients had a high CRP level, with a median value of 6.95 mg/dl (range=4.01-28.51 mg/dl), while 77 patients had a low CRP

Table II. Univariate Cox proportional hazards analysis of clinicopathological factors for overall survival of patients with esophageal cancer.

Factor	Number of patients (%)	HR	95% CI	p-Value
Age				
>66 Years	58 (50.4%)	1.000		
≤66 Years	57 (49.6%)	1.116	0.552-2.260	0.760
Gender				
Female	23 (20.0%)	1.000		
Male	93 (80.0%)	1.847	0.646-5.280	0.252
Preoperative serum albumin				
>4.1 g/dl	49 (42.6%)	1.000		
≤4.1 g/dl	66 (57.4%)	1.309	0.634-2.704	0.466
ASA-PS				
1	17 (14.8%)	1.000		
2/3	98 (85.2%)	1.701	0.517-5.599	0.382
Lymph node dissection				
Three-field	93 (80.9%)	1.000		
Two-field	22 (19.1%)	1.470	0.513-4.212	0.474
Operative time				
≤400 min	59 (51.3%)	1.000		
>400 min	56 (48.7%)	1.399	0.689-2.841	0.353
Intraoperative blood loss				
≤420 ml	58 (50.4%)	1.000		
>420 ml	57 (49.6%)	1.216	0.600-2.466	0.587
Pathological T factor <sup>a</sup>				
T1-2	51 (44.3%)	1.000		
T3-4	64 (55.7%)	3.810	1.562-9.292	0.003
Pathological N factor <sup>a</sup>				
N0	42 (36.5%)	1.000		
N1-3	73 (63.5%)	2.245	0.963-5.236	0.061
Postoperative infectious complications <sup>b</sup>				
<Grade 3	95 (82.6%)	1.000		
≥Grade 3	20 (17.4%)	2.229	0.994-5.000	0.052
CRP on POD 4				
High	75 (65.2%)	1.000		
Low	40 (34.8%)	2.281	1.120-4.646	0.023

ASA-PS: American Society of Anesthesiologists Physical Status; HR: hazard ratio; CI: confidence interval; CRP: C-reactive protein; POD: Postoperative day. ASA-PS: <sup>a</sup>According to the Union for International Cancer Control (23). <sup>b</sup>According to Clavien–Dindo classification (25).

level with a median value of 1.50 mg/dl (range=0.13-3.99 mg/dl). The patients' demographic and clinical characteristics are summarized in Table I. The high CRP group had a longer operative time ( $p=0.006$ ), higher intraoperative blood loss ( $p=0.004$ ), and more frequent morbidity ( $p<0.001$ ) than did the group with a low CRP level.

**Survival analysis.** The median follow-up period was 41.2 months (range=18.3 to 75.9 months). The OS was significantly lower for the group with a high CRP ( $p=0.020$ , Figure 2). The 3- and 5-year OS rates were 62.8% and 57.5%, respectively, in the high CRP group and 81.3% and 70.5%, respectively, in the group with low CRP. Each of the clinicopathological factors were categorized as shown in Table II and analyzed to determine their prognostic significance. The univariate and multivariate analyses demonstrated that pathological T3/4 and high CRP level on POD 4 were significant independent risk factors for poorer OS (Tables II and III).

The RFS differed significantly between the two groups ( $p=0.001$ , Figure 3). The 3- and 5-year RFS rates were 37.6% and 37.6%, respectively, in the high CRP group and 69.5% and 69.5%, respectively, in the group with low CRP. The clinicopathological factors were analyzed to determine their prognostic significance. The results of univariate and multivariate analyses demonstrated that pathological N1/2/3 and high CRP level on POD 4 were significant independent risk factors for poorer RFS (Tables III and IV).

## Discussion

The present study examined whether early changes in the postoperative serum CRP level had a survival impact in patients with advanced esophageal cancer who received neoadjuvant chemotherapy followed by curative resection with perioperative steroid therapy and ERAS care. The major finding of this study was that a CRP level exceeding 4.0 mg/dl

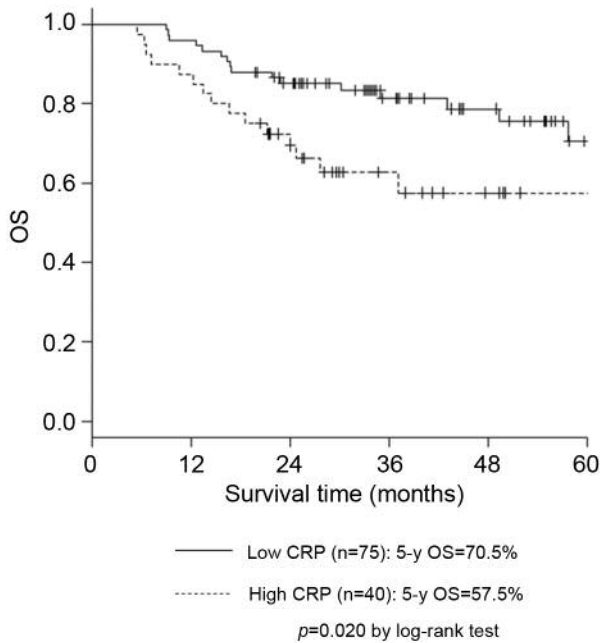


Figure 2. Kaplan–Meier curve for overall survival in patients with esophageal cancer according to C-reactive protein (CRP) level on postoperative day 4 (high CRP:  $\geq 4.0$  mg/dl, low CRP:  $< 4.0$  mg/dl).

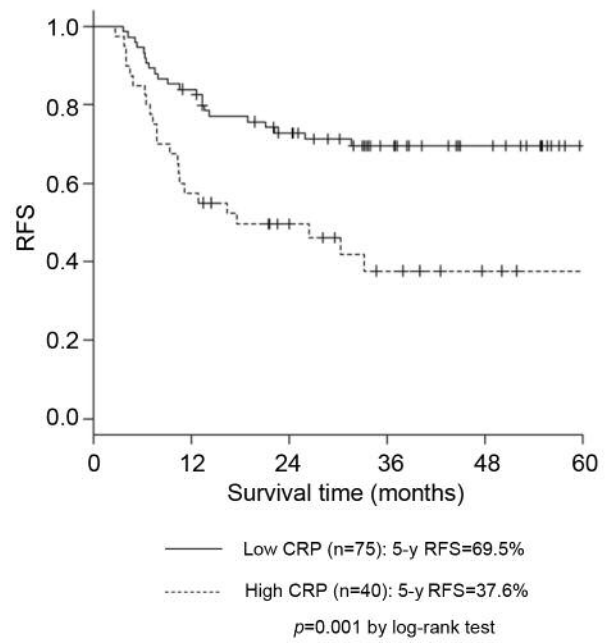


Figure 3. Kaplan–Meier curve for recurrence-free survival in patients with esophageal cancer according to C-reactive protein (CRP) level on postoperative day 4 (high CRP:  $\geq 4.0$  mg/dl, low CRP:  $< 4.0$  mg/dl).

Table III. Multivariate Cox proportional hazards analysis of clinicopathological factors for overall (OS) and recurrence-free (RFS) survival of patients with esophageal cancer.

Factor	Number of patients (%)	OS			RFS		
		HR	95% CI	p-Value	HR	95% CI	p-Value
Pathological T factor <sup>a</sup>							
T1-2	51 (44.3%)	1.000		0.003			
T3-4	64 (55.7%)	3.846	1.574-9.399				
Pathological N factor <sup>a</sup>							
N0	42 (36.5%)				1.000		<0.001
N1-3	73 (63.5%)				4.226	1.880-9.499	
CRP on POD 4							
High	75 (65.2%)	1.000		0.022	1.000		<0.001
Low	40 (34.8%)	2.323	1.129-4.777		2.909	1.612-5.249	

ASA-PS: American Society of Anesthesiologists Physical Status; HR: hazard ratio; CI: confidence interval; CRP: C-reactive protein; POD: postoperative day. ASA-PS: <sup>a</sup>According to the Union for International Cancer Control (23).

on POD 4, which had been previously reported to be an indicator of postoperative infectious complications (26), was useful for predicting long-term outcomes in such patients. Therefore, the present results suggest that poorer survival is at least in part dependent on the magnitude of the postoperative systemic inflammatory response, even in patients who have received perioperative steroid therapy and ERAS care.

The clinical impact of the postoperative serum CRP level in patients with esophageal cancer has been reported previously

(15,16). In the present study, the hazard ratio (HR) for RFS was 2.558 [95% confidence interval (CI)=1.422-4.602] and that for OS was 2.281 (95% CI=1.120-4.646). A similar HR and 95% CI were obtained in previous studies. Ibuki *et al.* studied 202 patients with esophageal cancer and found that the postoperative serum CRP level was independently associated with worse overall survival (HR=2.45, 95% CI=1.50-3.99) (15). In addition, Matsuda *et al.* studied 215 patients with esophageal cancer and found that the postoperative serum CRP

Table IV. Univariate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival of patients with esophageal cancer.

Factor	Number of patients (%)	HR	95% CI	p-Value
Age				
>66 Years	58 (50.4%)	1.000		
≤66 Years	57 (49.6%)	1.255	0.698-2.255	0.448
Gender				
Female	23 (20.0%)	1.000		
Male	93 (80.0%)	1.538	0.686-3.447	0.296
Preoperative serum albumin				
>4.1 g/dl	49 (42.6%)	1.000		
≤4.1 g/dl	66 (57.4%)	1.214	0.668-2.204	0.525
ASA-PS				
1	17 (14.8%)	1.000		
2/3	98 (85.2%)	1.148	0.486-2.712	0.753
Lymph node dissection				
Three-field	93 (80.9%)	1.000		
Two-field	22 (19.1%)	0.754	0.373-1.523	0.432
Operation time				
≤400 min	59 (51.3%)	1.000		
>400 min	56 (48.7%)	1.746	0.961-3.171	0.067
Intraoperative blood loss				
≤420 ml	58 (50.4%)	1.000		
>420 ml	57 (49.6%)	1.643	0.909-2.971	0.100
Pathological T factor <sup>a</sup>				
T1-2	51 (44.3%)	1.000		
T3-4	64 (55.7%)	2.207	1.158-4.208	0.016
Pathological N factor <sup>a</sup>				
N0	42 (36.5%)	1.000		
N1-3	73 (63.5%)	3.766	1.681-8.439	0.001
Postoperative infectious complications <sup>b</sup>				
<Grade 3	95 (82.6%)	1.000		
≥Grade 3	20 (17.4%)	1.532	0.737-3.187	0.253
CRP on POD 4				
High	75 (65.2%)	1.000		
Low	40 (34.8%)	2.558	1.422-4.602	0.002

ASA-PS: American Society of Anesthesiologists Physical Status; HR: hazard ratio; CI: confidence interval; CRP: C-reactive protein; POD: postoperative day. ASA-PS: <sup>a</sup>According to the Union for International Cancer Control (23). <sup>b</sup>According to Clavien–Dindo classification (25).

was independently associated with worse overall survival (HR=2.196, 95% CI=1.250-3.857) (16). Thus, the postoperative serum CRP level had a clinical impact on the survival of patients with esophageal cancer. However, these studies included patients with early esophageal cancer as well as patients who received no neoadjuvant therapy, which most likely affected the results. To our knowledge, ours is the first study to report on patients with advanced esophageal cancer who received neoadjuvant chemotherapy followed by curative resection with perioperative steroid therapy and ERAS care.

There are several possible reasons why a high CRP level affects the survival of patients with esophageal cancer. One possible reason for this association is that the CRP level might be associated with postoperative surgical complications (26). In fact, the incidence of postoperative infectious complications was higher in the group with a low CRP level

than in the high CRP group. We previously investigated the impact of postoperative complications on OS and disease-free survival in 111 patients who underwent curative surgery for esophageal cancer (12). The OS rate 5 years after surgery was 34.1% in patients with postoperative complications and 77.6% in the patients without postoperative complications. This difference was statistically significant ( $p=0.005$ ). The multivariate analysis demonstrated that postoperative complications were a significant independent risk factor for poorer OS and disease-free survival. Another possible reason for this association is that the patients who were in the group with a high CRP level might have had some factors that led to decreased immunity against their tumors. Goldfarb *et al.* reported that treatment aimed to perioperatively enhance cell-mediated immunity by simultaneously inhibiting excessive catecholamine and prostaglandin responses was successful in

limiting postoperative immune suppression and metastatic progression in rodent models of cancer (28). In addition, Dunn *et al.* suggested that the adaptive immune system might function by identifying and eliminating nascent tumor cells in experimental models (29).

The cut-off CRP value was 4.0 mg/dl on POD 4 in the present study. As compared with previous studies examining the utility of CRP for predicting survival, our surgical approach was highly invasive, but the operative time and blood loss were similar (9, 30). However, the cut-off CRP value in our study was much lower than that in previous studies, in which the CRP value ranged from 8.6 to 15.0 mg/dl [15-18]. The low cut-off CRP value in our study may be explained by our use of steroid therapy and ERAS, which helped reduce surgical stress-induced inflammatory responses (19-22). Several studies reported that the postoperative CRP level was reduced to nearly half in patients who underwent esophagectomy and received perioperative steroid therapy (20, 21). Furthermore, Chen *et al.* found that postoperative CRP levels on POD 1, 3, and 7 were significantly lower in patients who received perioperative care with fast-track surgery than in other patients (22).

Our study has several potential limitations. Firstly, it was a retrospective single-center study with a small sample size. Secondly, there was no standard type, period, or dose of perioperative steroid therapy. The perioperative ERAS program also differed by hospital. Thus, the cut-off CRP value most likely differed depending on the perioperative management regimen used by a given hospital. In addition, our hospital is a specialized cancer center. To confirm the present results, a large prospective study is necessary.

In conclusion, the magnitude of the postoperative systemic inflammatory response was associated with oncological outcomes after surgery in patients with advanced esophageal cancer who received neoadjuvant chemotherapy followed by curative resection with perioperative steroid therapy and ERAS care. To improve the survival of patients with esophageal cancer, it is necessary to carefully plan surgical procedures and perioperative care, and to select the optimal surgical strategy to attenuate the systemic inflammatory response.

### Conflicts of Interest

The Authors declare no conflict of interest in regard to this study.

### Authors' Contributions

KK, TA, TY, TO and TO made substantial contributions to conception and design. KK, TA, YM, TH, TY, TS, HC, TY, TO and TO made substantial contributions to acquisition of data, or analysis and interpretation of data. KK, TA, YM, TH, TY, HT, TS, HC, TY, TO and TO were involved in drafting the manuscript or revising it critically for important intellectual content. YR, MM, TO and TO gave final approval of the version to be published. Each Author participated sufficiently in the work to take public responsibility for appropriate

portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Authors read and approved the final manuscript.

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