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The seven-day cumulative post-esophagectomy inflammatory response predicts cancer recurrence

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Abstract

Background The relationship between postoperative cumulative systemic inflammation and cancer survival needs to be investigated. We developed an approach to the prognostication of postoperative esophageal cancer by establishing low and high cut-off values for the C-reactive protein (CRP) area under the curve (AUC) at 7 and 14 days after esophagectomy.

Methods One hundred and twenty-five consecutive patients with biopsy-proven invasive esophageal squamous cell carcinoma (SCC) who underwent esophagectomies were evaluated. Postoperative CRP levels were analyzed for the first 14 days after surgery. The AUC on days 7 and 14 were calculated and compared with clinicopathological features and survival. The cut-off values for CRP at 7 days (CRP 7 d) and 14 days (CRP 14 d) were 599 mg/L and 1153 mg/L, respectively.

Results The patients in the low CRP 7 d group had significantly better recurrence-free survival (RFS) and overall survival (OS), not that in the low CRP 14d group. The OS rates in the high CRP groups at PODs 1, 3, 10, and 14 were significantly lower than those in the low CRP groups. Postoperative complications were more common in the high CRP groups on PODs 3, 10, and 14. Univariate analyses revealed that pTNM stage, depth of tumor invasion, tumor location, lymph node involvement, and CRP 7 d were significant prognostic factors for both OS and RFS. The Cox proportional hazards model identified pTNM, tumor location, and CRP 7d as independent prognostic factors for the RFS and OS.

Conclusions Early prediction of patients with postoperative complications, and adequate management will suppress the elevation of CRP 7 d and further suppress the CRP value in the late postoperative period, which may improve the prognosis of esophageal cancer patients after esophagectomy.

Keywords Esophagectomy, Esophageal cancer, CRP, Prognosis, Complications

Background

Esophageal cancer is the tenth most common cancer, with 604,100 new cases worldwide. The fatality rate in 2020 was 544,076 cases [1]. Surgery is the standard treatment for patients with locoregional disease. Two-thirds of patients with esophageal cancer have advanced disease at diagnosis [2], and there is a high rate of recurrence, even after curative surgery [3–6]. Esophagectomy is a highly invasive procedure with several serious postoperative

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complications, including pneumonia, anastomotic leakage, and recurrent laryngeal nerve paralysis [7–9]. Previous studies showed that the postoperative complications worsen the prognosis in esophageal cancer patients [10–14]. C-reactive protein (CRP), which is synthesized in the liver, is a sensitive indicator of the systemic inflammatory response(SIR), which is stimulated by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α (TNF-α) from tumor cells [15]. High concentrations of CRP are associated with high mortality, poor response to treatment, and recurrence of solid tumors [16]. Some studies have reported the association between postoperative CRP levels, complications, and prognosis [17–22]. However, these studies evaluated CRP level at one point on the postoperative day, and the timings of CRP evaluation were inconsistent, ranging from 1 PODs(Postoperative Day) to 2 months. If postoperative complications could be predicted by using CRP values on early postoperative period, it would be clinically very useful and would lead to treatment. Furthermore, indicators are needed to comprehensively evaluate the results of interventions for postoperative complications. Therefore, we thought of comprehensively evaluating the postoperative inflammatory response by graphing the postoperative CRP values and integrating the area under the curve (AUC). In the present study, to examine whether postoperative complications can be predicted by CRP values in early postoperative period, and we quantified CRP for 2 weeks after surgery, analyzed the relationships between cumulative CRP levels (early and late phase) and postoperative complications, and evaluated the clinical significance of postoperative CRP levels over time as a prognostic factor.

Methods

One hundred and seventy-three patients with esophageal cancer or cancer or esophagogastric junction aged 20–80 years old were enrolled in this study. They received surgery at Kawasaki Medical School Hospital between January 2010 and June 2021, and their patients' records were reviewed retrospectively. The patients were received esophagectomy with/or two or three field lymphadenectomies or total gastrectomy + lower esophagectomy was performed. Adenocarcinoma of the esophagus or esophagogastric junction, other types of cancer(small cell carcinoma), R2 resection, and combined other malignancy (advanced gastric cancer: two patients, head and neck cancer: seven patients) were excluded in this study. Total 125 patients were analyzed in this study (Fig. 1). Tumor staging was based on the

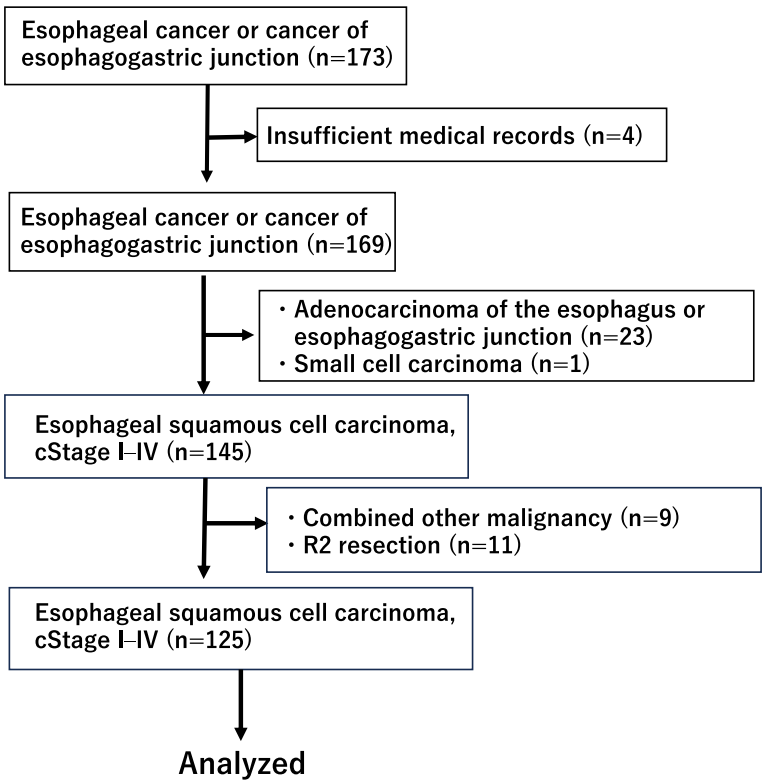

Fig. 1 The patients flow diagram in this study

UICC classification of malignant tumors (8th edition) [23]. Two or three cycles of neoadjuvant therapy consisting of 5-FU/cisplatin or 5FU/cisplatin/docetaxel were administered to nine cStage II/III cases after 2017, with esophagectomy conducted at 3–7 weeks after completion of chemotherapy. Transthoracic esophagectomy with two- or three-field lymph node dissections and esophageal reconstruction was performed using a gastric tube in the retrosternal or posterior mediastinal roots. A few patients underwent right side colon replacement in the retrosternal root. Thoracoscopic and laparoscopic-assisted approaches were also utilized. Trans-hiatal esophagectomy with middle, lower mediastinal, and abdominal lymphadenectomy was performed in cStage I cases. The details of these procedures were described in a previous report [24]. The present study was approved by the Institutional Review Board of Kawasaki Medical School (Authorization No: 5603–03). Data were collected from the medical records at Kawasaki Medical School Hospital, and details of this retrospective study were provided on the hospital's home page. All patients were followed up regularly until November 2023 or death. Informed consent was obtained from all patients preoperatively. Routine laboratory measurements of preoperative CRP were performed at 1–4 weeks before surgery. In the nine patients who received neoadjuvant chemotherapy, the CRP measurements were performed at 3–5 days before surgery.

Evaluation of postoperative CRP

CRP was measured routinely on postoperative days (PODs) 1, 2, 3, 5, 7, 10, and 14. Additional measurements were performed according to each patient's condition. CRP was measured using anti-human CRP mouse monoclonal antibody-sensitive latex (SEKISUI, Tokyo, Japan), with a normal cut-off value of 1.4 mg/L. The CRP values for 14 days after surgery were graphed using commercial software (Microsoft Excel 2019; Microsoft Inc., Redmond WA, USA) to create a curve trendline (Fig. 2). The area under the curve (AUC) trendline was calculated by definite integrals. CRP at 7 days (CRP 7 d) was defined as the cumulative CRP value for 7 days after surgery, and CRP at 14 days (CRP 14 d) was defined as the cumulative CRP value for 14 days after surgery. Four patients were excluded because of data unavailability for the CRP 14 d analysis. Also, CRPmax was evaluated in this study.

Postoperative complications

Significant postoperative complications were evaluated and classified according to the Clavien–Dindo classification as grade ≥ 2 [25]. In addition, we also investigated the patients with grade ≥ 3.

Statistical analysis

Overall survival (OS) was defined as the time between surgery and patient death or the availability of final information on vital status. Recurrence-free survival (RFS) was defined as the time between surgery and cancer recurrence or death. A time-dependent receiver operating characteristic curve was generated to evaluate the sensitivity and specificity of CRP 7 d, CRP 14 d, and CRP on PODs 1, 2, 3, 5, 7, 10, and 14 for predicting 3-year OS. Youden's index was calculated to determine the optimal cut-off values for these parameters. The cut-off

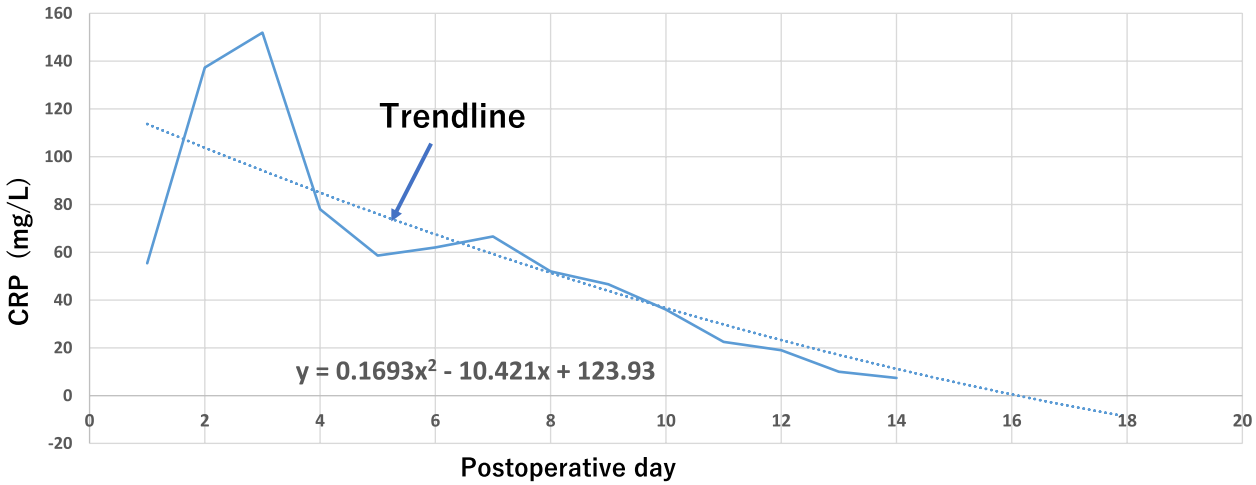

Fig. 2 The CRP values (mg/L) on postoperative days. The trendline was created by Microsoft EXCEL (Dotted line). After then, area under the trendline as calculated by integral calculus

Table 1 Clinical characteristics of low- and high-CRP 7 d groups

Covariates	Low CRP 7 d	High CRP 7 d	*P*
n	39	86	
Age, y:Median			
< 67	22	42	0.448
> 67	17	44	
Sex			
Male	30	76	0.112
Female	9	10	
Tumor location			
Upper	6	20	0.309
Middle	25	42	
Lower	8	24	
Tumor length			
< 50 mm	20	40	0.7
> 50 mm	19	46	
pTNM**			
I	19	27	0.182
II	3	15	
III	13	28	
IV	4	16	
pT			
T1	24	39	0.338
T2	4	11	
T3	10	28	
T4	1	8	
pN			
pN0	19	35	0.868
pN1	9	23	
pN2	6	17	
pN3	5	11	
****M-factor			
M0	37	81	1
M1	2	5	
Procedure			
Ivor Lewis	4	15	0.63
Thoracoscopic	30	62	
***THE	5	9	
Blood loss	150 g	180 g	0.207
Operation time	373 min	372.5 min	0.747
preoperative CRP	0.8 mg/L	1.7 mg/L	*0.0001
Neoadjuvant chemotherapy			1
(-)	36	80	
(+)	3	6	
Postoperative complications (Grade≥II)			0.0816
(-)	24	37	
(+)	15	49	
Anastomotic leakage			*0.0334
(-)	37	68	
(+)	2	18	
Recurrent nerve palsy			0.583

Table 1 (continued)

Covariates	Low CRP 7 d	High CRP 7 d	*P*
(-)	32	75	
(+)	7	11	
Respiratory complications			0.106
(-)	34	63	
(+)	5	23	
SSI(Surgical Site Infection)			0.106
(-)	34	63	
(+)	5	23	
Postoperative complications(Grade≥III)			
(-)	28	42	*0.02
(+)	11	44	

*Statistically significant

**pTNM: pathological TNM

***THE: Transhiatal esophagectomy

****M-factor: Distant metastasis

value of CRPmax was evaluated similarly. The chi-square test or Fisher's exact test was used for categorical variables. The Mann–Whitney U-test was used for continuous variables. The Kaplan–Meier method was employed to estimate survival, and groups were compared using a two-sided log-rank test. Univariate and multivariate analyses for OS and RFS were performed using the Cox proportional hazards regression model, and the survival rate with 95% confidence interval (CI) was determined. Covariates for the Cox model were selected based on age and gender plus the following criteria: (i) the number of explanatory variables was approximately one-tenth the number of event occurrences; (ii) factors dependent on each other (collinearity) were not entered; (iii) useful independent prognostic factors were selected from previously published data, and factors with $P<0.2$ in the univariate analyses were permitted. Statistical analyses were performed using commercial (JMP version 14; SAS, Tokyo, Japan) and open-source (R version 3.1.1; R Project for Statistical Computing, Vienna, Austria) software.

Results

The cut-off values for CRP 7 d and CRP 14 d were 599 mg/L (specificity: 0.409; sensitivity: 0.797; AUC: 0.56) and 1153 mg/L (specificity: 0.484; sensitivity: 0.702; AUC: 0.579), respectively. Based on these cut-off values, CRP 7 d and CRP 14 d were each divided into two groups (low and high CRP groups). The cut-off value of CRPmax was 16.17 mg/dL.

Patient characteristics

The mean follow-up time was 3.5 years. Table 1 summarizes the relationships between CRP 7 d and clinicopathological features in the patients. Preoperative CRP levels were significantly higher in the high CRP 7 d group ($P<0.001$). Postoperative complications of grade ≥ 3 were more common in the high CRP7d group ($P=0.02$), and anastomotic leakage was also more frequent in the high CRP7d group ($P=0.0334$). Table 2 summarizes the relationships between CRP 14 d and clinicopathological features in the patients. Preoperative CRP levels were significantly higher in the high CRP 14 d group ($P=0.001$). Postoperative complications with Grade ≥ 2 and 3 were more common in the high CRP 14 d group ($P=0.0008$). Patients with anastomotic leakage, respiratory complications, and SSI were more likely to be in the high CRP14d group ($P=0.048$, 0.0175, 0.0272, respectively).

Survival in the CRP 7 d groups

Overall, 59 patients had cancer recurrence and 49 patients died during the follow-up period. The 3- and 5-year RFS rates were 73.4% and 61.9% in the low CRP 7 d group and 49.6% and 40.9% in the high CRP 7 d group, respectively ($P=0.0117$) (Fig. 3A). The 3- and 5-year OS rates were 81.8% and 74.6% in the low CRP 7 d group and 54.5% and 47.8% in the high CRP 7 d group, respectively ($P=0.0087$) (Fig. 3B).

Survival in the CRP 14 d groups

The 3- and 5-year RFS rates were 68% and 64.3% in the low CRP 14 d group and 50.7% and 40.5% in the high

Table 2 Clinical characteristics of low- and high-CRP 14 d groups

Covariates	Low CRP 14d	High CRP 14d	*p*-value
n	49	72	
Age (y):Median			
< 67	26	34	0.581
> 67	23	38	
Sex			
Male	37	65	*0.041
Female	12	7	
Tumor location			
Upper	7	18	0.195
Middle	31	34	
Lower	11	20	
Tumor length			
< 50 mm	23	36	0.853
> 50 mm	26	36	
**pTNM			
I	23	22	0.366
II	6	12	
III	14	26	
IV	6	12	
pT			
pT1	30	31	0.223
pT2	4	11	
pT3	12	26	
pT4	3	4	
pN			
pN0	24	28	0.766
pN1	11	20	
pN2	8	14	
pN3	6	10	
****M-factor			
M0	47	67	0.7
M1	2	5	
Procedure			
Ivor Lewis	6	11	0.908
Thoracoscopic	37	53	
***THE	6	8	
Blood loss	150 g	200 g	0.278
Operation time	375 min	377 min	0.804
Preoperative CRP	0.8 mg/L	1.8 mg/L	*0.001
Neoadjuvant chemotherapy			1
(-)	45	67	
(+)	4	5	
Postoperative complications(Grade≥2)			*0.0008
(-)	33	25	
(+)	16	47	
Anastomotic leakage			*0.048
(-)	45	56	
(+)	4	16	
Recurrent nerve palsy			0.294

Table 2 (continued)

Covariates	Low CRP 14d	High CRP 14d	*p*-value
(-)	40	64	
(+)	9	8	
Respiratory complications			
(-)	41	33	*0.0175
(+)	6	18	
SSI(Surgical Site Infection)			*0.0272
(-)	43	50	
(+)	6	22	
Postoperative complications(Grade≥3)			*0.0001
(-)	38	28	
(+)	11	44	

*Statistically significant

**pTNM: pathological TNM

***THE: Transhiatal esophagectomy

****M-factor: Distant metastasis

CRP 14 d group, respectively, with no significant difference ($P=0.132$) (Fig. 4A). The 3- and 5-year OS rates also showed no significant difference ($P=0.111$) (Fig. 4B).

Survival for patients with or without postoperative complications

Postoperative complications of grade ≥2 were noted in 66 of the 125 patients.

No significant differences were found in OS and RFS with or without postoperative complications (Fig. 5A,B).

Univariate analyses for patients with or without postoperative complications based on CRP 7 d and CRP 14 d

The low CRP 7 d group tended to be better RFS than the high CRP 7 d group with postoperative complications ($P=0.075$, Table 3A). The low CRP 7 d group had significantly better OS than the high CRP 7 d group ($P=0.032$, Table 3B).

Relationships between postoperative CRP values and survival or complications

The postoperative CRP values at PODs 1, 2, 3, 5, 7, 10, and 14 are shown in Fig. 6. The cut-off values for these parameters and the survival rates in the high and low CRP groups are shown in Table 4. The OS rates in the high CRP groups at PODs 1, 3, 10, and 14 were significantly lower than those in the low CRP groups ($P=0.0190$, $P=0.019$, $P=0.014$, and $P=0.032$, respectively). The RFS rates in the high CRP groups at PODs 1, 10, and 14 were significantly lower than those in the low CRP groups ($P=0.006$, $P=0.012$, and $P=0.004$, respectively). The high CRP group of Day 3 tended to be worse survival compared to the low group ($P=0.063$). The relationship between postoperative CRP levels and complications was analyzed. Postoperative complications were more common in the high CRP groups on PODs 3, 10, and 14 ($P=0.0068$, $P=0.0066$, and $P=0.00049$, respectively).

Univariate and multivariate Cox analyses

The univariate analyses revealed that pTNM stage, depth of tumor invasion, tumor location, extent of lymph node involvement, and CRP 7 d value were significant prognostic factors for both OS and RFS in patients with resectable esophageal cancer (Table 5). The Cox proportional hazards model for preoperative or postoperative clinicopathological factors and CRP 7 d identified pTNM, tumor location and CRP 7 d as independent prognostic factors for RFS and OS(Table 6).

Discussion

This study attempted to evaluate postoperative CRP levels using an AUC method with definite integrals. CRP 7 d was identified as a significant prognostic factor in both univariate and Cox analysis. Furthermore, a detailed analysis of postoperative CRP levels revealed that CRP levels on PODs 1, 3, 10, and 14 were associated with prognosis, and postoperative complications were more common in the high CRP group on PODs 3, 10, and 14. In this study, we excluded esophageal and esophagogastric junction adenocarcinoma because surgical procedures for adenocarcinoma are less consistent than for squamous cell carcinoma, and because many adenocarcinoma patients are obese, which is estimated to lead to higher postoperative CRP levels.

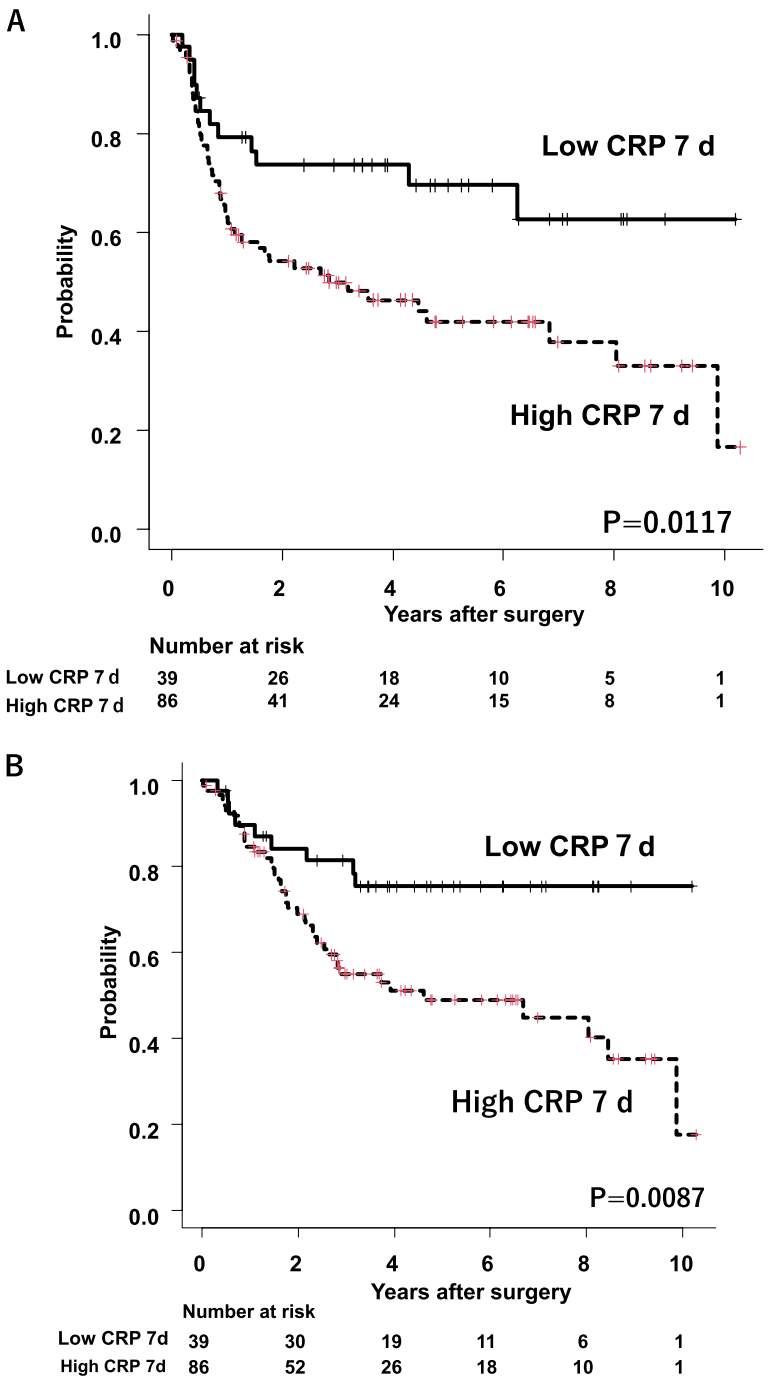

Fig. 3 **A** Recurrence-free survival in the low and high CRP 7 d groups after esophagectomy. The low CRP 7 d group had significantly better survival than the high CRP 7 d group ($P=0.0117$). **B** Overall survival between low and high CRP 7 d groups after esophagectomy. Low CRP 7 d group was significantly better survival than high CRP 7 d group ($P=0.0087$)

There have been some reports on postoperative CRP levels in esophageal cancer patients [17–22, 26]. These studies evaluated the postoperative CRP using different methods to predict postoperative complications or prognosis. Matsuda et al. [18] reported that an intense postoperative inflammatory response, consisting of a delayed CRP peak (POD 3 or later) and persistent CRP elevation, was associated with a poor

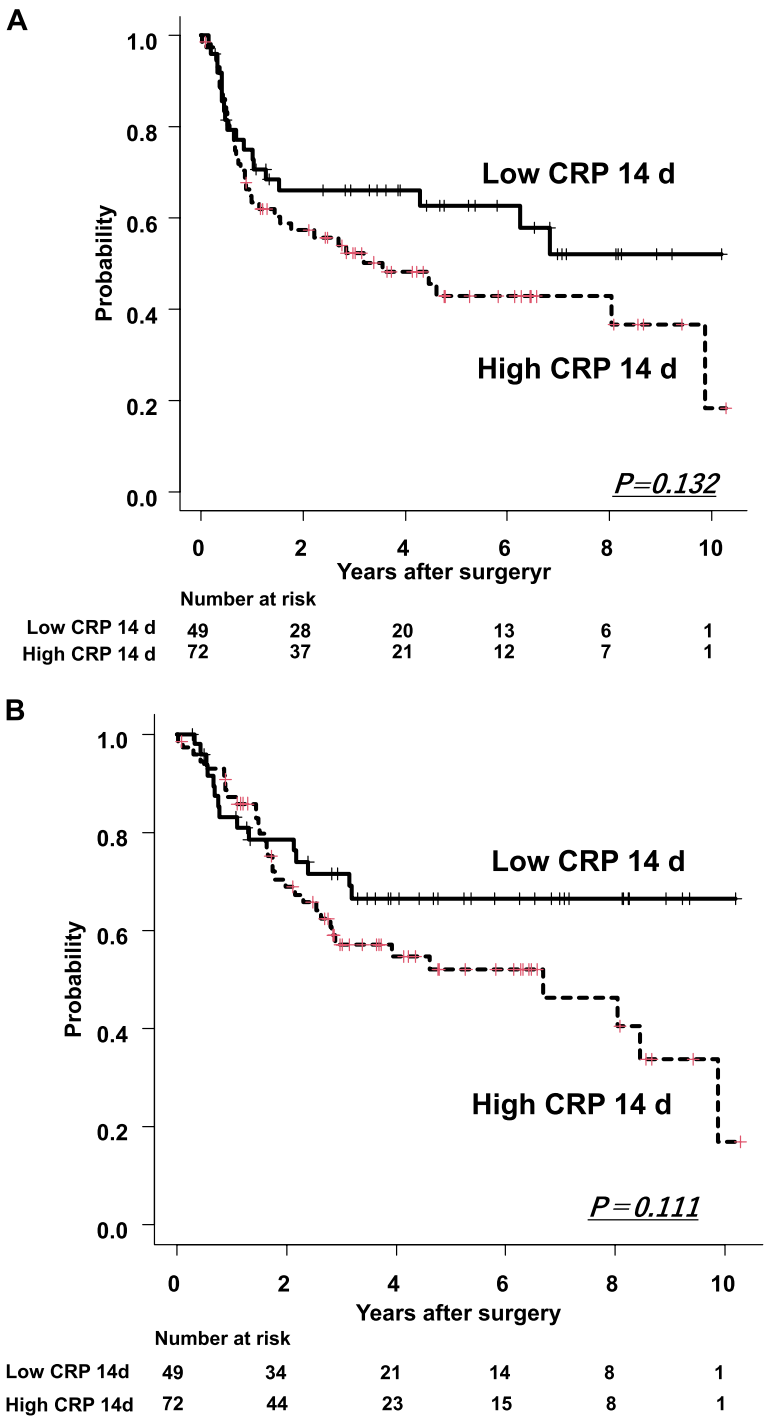

Fig. 4 **A** Recurrence-free survival between low and high CRP 14 d groups after esophagectomy. Low CRP 14 d group was tendency to be better survival than high CRP 14 d group, but not significantly difference ($P=0.132$). **B** Overall survival between low and high CRP 14 d groups after esophagectomy. Low CRP 14 d group tended to have better survival than the high CRP 14 d group, but not to a significant degree ($P=0.111$)

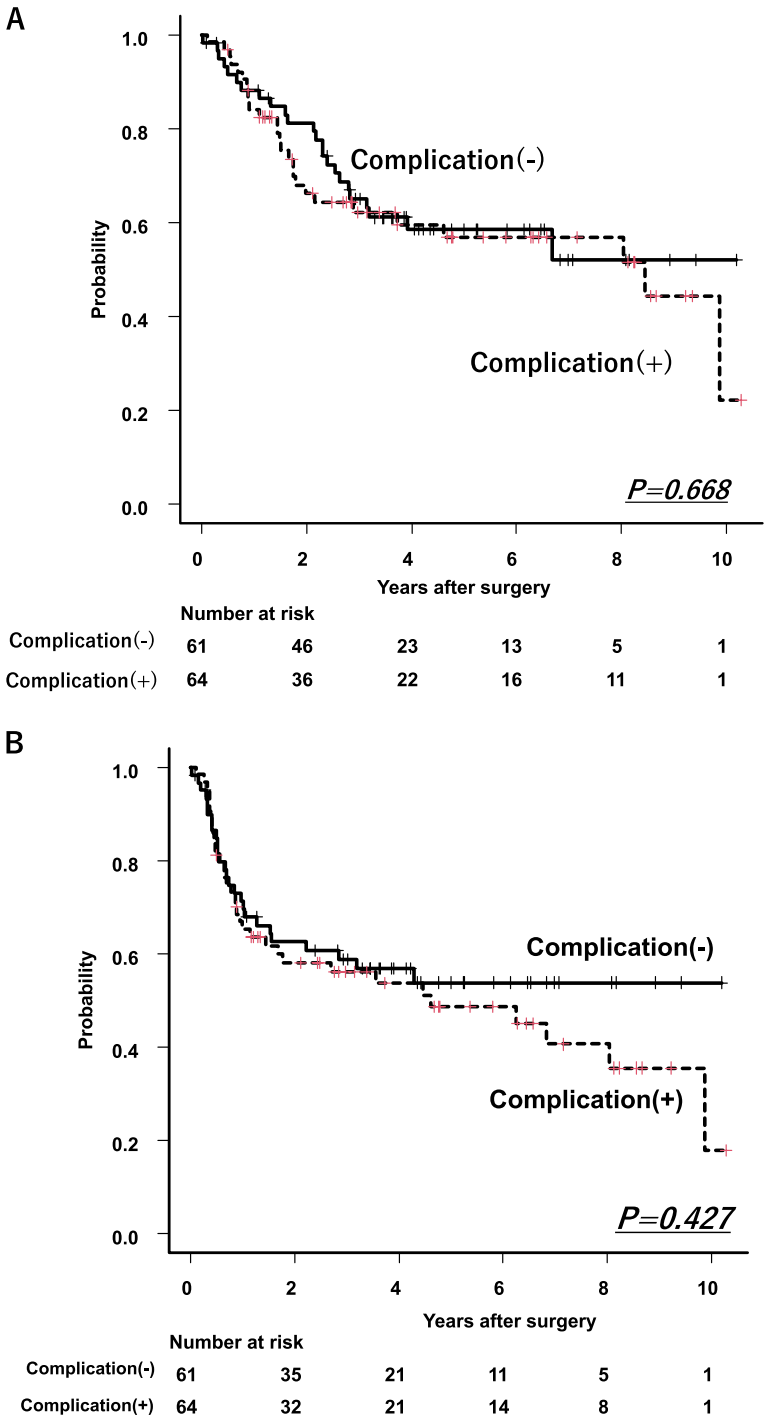

Fig. 5 **A** Overall survival between with and without postoperative complications ≥ Grade 2. No significant differences between two groups ($P = 0.668$). **B** Recurrence free survival between with and without postoperative complications ≥ Grade2. No significant differences between two groups ($P = 0.427$)

Table 3 Univariate analysis of OS and RFS in ESCC patients after esophagectomy with or without complications

A Univariate analysis of OS and RFS in ESCC patients after esophagectomy with complications						
		RFS			OS	
Variables	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Postoperative CRP 7d Low vs High	2.371	0.913–6.157	0.075	1.848	0.633–5.398	0.261
Postoperatve CRP 14d Low vs High	2.112	0.863–5.170	0.102	2.097	0.716–6.136	0.177
B Univariate analysis of OS and RFS in ESCC patients after esophagectomy without complications						
		RFS			OS	
Variables	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Postoperative CRP 7d Low vs High	1.97	0.822–4.423	0.128	2.961	1.097–7.991	*0.032
Postoperatve CRP 14d Low vs High	1.073	0.480–2.397	0.864	1.259	0.545–2.909	0.59

* Statistically significant

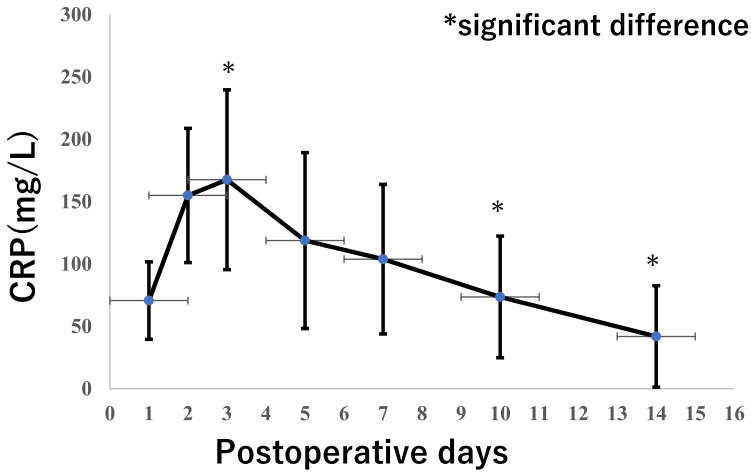

Fig. 6 Postoperative CRP values for 14 days after surgery. The values are expressed as mean ± SD. Postoperative complications were more common in PODs3,10,14 ($P=0.0068$, $P=0.0066$, $P=0.00049$)

prognosis. However, their report did not assess the amount and sustained changes in CRP levels postoperatively. Other studies evaluated the postoperative CRP levels at a single point after esophagectomy, which was different from our report and that of Matsuda et.al. As a biomarker for predicting complications, it has been reported that postoperative complications were more likely to occur in the high CRP group on PODs 2–4 [17, 19, 21]. We similarly found that postoperative complications were more likely to occur in the high CRP group at PODs3, and it was noted that the patients with postoperative complications were more common in the high CRP group at PODs10.14. These findings suggested that early postoperative CRP levels(> 141 mg/L) can predict postoperative complications and insufficient treatment or delayed treatment effect for complications may have caused a delay in the inflammatory response. In the present study, we created a curve trendline for postoperative CRP levels (PODs 1–14) and evaluated the AUC values, suggesting that CRP 7d was an independent prognostic factor in both OS and RFS. We hypothesized that continuous exposure to cytokines after radical surgery for esophageal cancer might activate microscopic cancer cells and cause postoperative recurrence. This is the first attempt to comprehensively evaluate postoperative CRP levels after surgery. In breast cancer, post-surgery wound fluid contains large amounts of cytokines and growth

Table 4 The cut-off values of postoperative CRP for Overall Survival(OS),and OS or Recurrence-free survival(RFS) between postoperative high and low CRP values after esophagectomy patients

	CRP:cut-off values(mg/L)	Sensityvity/specificity	AUC			
PODs1	89	0.853/0.388	0.611			
PODs2	168.7	0.649/0.455	0.521			
PODs3	140.9	0.453/0.714	0.532			
PODs5	69	0.297/0.872	0.568			
PODs7	72.1	0.439/0.795	0.609			
PODs10	55.9	0.547/0.767	0.603			
PODs14	24.2	0.576/0.711	0.583			
	For OS			**For RFS**		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
PODs1	2.017	1.122–3.625	0.019*	2.135	1.244–3.664	0.0006*
PODs2	1.279	0.705^2.318	0.417	1.095	0.64–1.871	0.741
PODs3	2.109	1.129–3.94	0.019*	1.676	0.971–2.894	0.063
PODs5	1.762	0.787–3.946	0.168	1.302	0.674–2.514	0.432
PODs7	1.734	0.878–3.426	0.1132	1.416	0.789–2.54	0.244
PODs10	2.305	1.181–4.499	0.014*	2.13	1.184–3.833	0.012*
PODs14	2.109	1.062–4.186	0.032*	2.456	1.333–4.525	0.004*

* Statistically significant for OS

factors and can promote the proliferation of breast cancer cells [27]. Hirai et al. [28]. reported that excessive surgical stress aggravated liver metastases in rat laparotomy and/or thoracotomy models. Studies on other tumors, including hepatocellular carcinoma and renal carcinoma, demonstrated that postoperative CRP levels affected the prognosis of these cancers [29, 30]. These findings imply that continuous exposure to inflammatory cytokines or excessive surgical stress contributes to cancer progression. Therefore, cumulative evaluation of CRP 7d and 14d is appropriate for postoperative CRP evaluation after esophagectomy.

Some papers have been published regarding postoperative CRP levels and prognosis [18–20, 22, 26]. Controversy has existed regarding the relationship between the timing of postoperative CRP evaluation and prognosis. Our data showed that OS was poor in the group with high CRP values PODs 1, 3, 10, and 14 days after surgery, but it is not possible to determine which period should be considered as important. Therefore, we believe that it is desirable to judge the postoperative CRP value comprehensively. In this study, CRP 7 d is a prognostic factor for esophageal cancer patients, while CRP 14 d is not. It is estimated that appropriate intervention may have been performed for patients who developed complications due to high CRP within one week after surgery, and as a result, CRP14 d decreased and did not become a prognostic factor. This may also be one of the reasons why the survival was not different between the presence or absence of postoperative complications. However, although many patients received appropriate treatment for postoperative complications and their CRP levels decreased, some cases were difficult to treat, and such cases may have insufficient CRP decreases and a worsened prognosis. Further examinations might be necessary.

The present study was limited by its retrospective design and the fact that postoperative CRP 7 d was an independent prognostic factor for esophageal cancer patients after esophagectomy both univariate and multivariate analysis. Furthermore, high CRP values at PODs 3 was associated with postoperative complications and poor prognosis. To prolong the survival of esophageal cancer patients, advances in surgical techniques and perioperative management are desired to prevent postoperative complications. Furthermore, it is necessary to pay attention to the CRP value on 3PODs in the early postoperative period, and take appropriate examinations to predict complications and interventions to decrease CRP 7d.

Conclusions

The cumulative postoperative CRP value for 1 week after surgery, designated CRP 7 d, was identified as an important prognostic factor after esophagectomy that may affect perioperative management. Attempts to

Table 5 Univariate analysis of overall survival (OS) and recurrence-free survival (RFS) in postoperative patients

		RFS			OS	
Variables	**Ratio**	**95% CI**	***p*-value**	**Ratio**	**95% CI**	***p*-value**
Age > 67 y	**1.031**	**0.621–1.714**	**0.904**	**1.078**	**0.621–1.871**	**0.789**
Gender (Male:Female)	**1.233**	**0.624–2.438**	**0.5471**	**1.156**	**0.542–2.464**	**0.7074**
pTNM Stages (I:II:III:IV)	**1.646**	**1.294–2.094**	**0.0001***	**1.724**	**1.32–2.251**	**0.0001***
Depth of tumor invasion (T1:T2:T3:T4)	**1.529**	**1.212–1.929**	**0.0001***	**1.568**	**1.218–2.026**	**0.0005***
Lymph nodes metastasis (N0:N1: N2:N3)	**1.636**	**1.292–2.073**	**0.0001***	**1.755**	**1.352–2.278**	**0.0001***
Distant metastasis (M0:M1)	**1.014**	**0.364–2.825**	**0.979**	**1.037**	**0.369–2.908**	**0.9456**
Tumor size (≥ 50 mm)	**1.156**	**0.695–1.927**	**0.5735**	**1.202**	**0.692–2.089**	**0.5133**
Tumor location (Upper:Middle,Lower)	**0.588**	**0.399–0.866**	**0.0072***	**0.592**	**0.392–0.894**	**0.0126***
Preoperative CRP (> 1.4 mg/L)	**1.479**	**0.874–2.505**	**0.145**	**1.634**	**0.917–2.912**	**0.096**
Postoperative CRP 7 d (Low:High)	**2.214**	**1.174–4.140**	**0.0140***	**2.542**	**1.235–5.233**	**0.0113***
Postoperative CRP 14 d (Low:High)	**1.521**	**0.877–2.637**	**0.135**	**1.633**	**0.888–3.004**	**0.115**
Postoperative complications(≥ Grade2) (Yes:No)	**1.23**	**0.737–2.052**	**0.428**	**1.129**	**0.649–1.963**	**0.668**
Anastomotic leakage (Yes:No)	**1.297**	**0.682–2.465**	**0.428**	**1.043**	**0.502–2.191**	**0.9**
Respiratory complications (Yes:No)	**1.495**	**0.850–2.626**	**0.163**	**1.462**	**0.775–2.756**	**0.2408**
SSI (Superficial and deep) (Yes:No)	**1.087**	**0.603–1.961**	**0.781**	**0.882**	**0.448–1.734**	**0.716**
Postoperative complications (≥ Grade III) (Yes:No)	**1.464**	**0.880–2.436**	**0.143**	**1.398**	**0.804–2.431**	**0.236**
CRPmax (Low:High)	**1.272**	**0.752–2.152**	**0.37**	**1.455**	**0.8111–2.61**	**0.208**

* Statistically significant

Table 6 Cox analysis of Recurrence-free Survival (RFS) and Overall Survival (OS) in ESCC patients after esophagectomy

		OS			RFS	
Variables	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age > 67 y	**0.9**	**0.512–1.583**	**0.7148**	**0.837**	**0.4951–1.416**	**0.5073**
Gender (Male:Female)	**0.936**	**0.422–2.077**	**0.8714**	**1.09**	**0.529–2.245**	**0.8157**
pTNM (I,II/III,IV)	**4.147**	**2.139–8.04**	**0.00001***	**4.383**	**2.37–8.106**	**0.00001***
Location (Upper/Middle,Lower)	**0.372**	**0.196–0.707**	**0.00254***	**0.304**	**0.163–0.569**	**0.000195***
CRP d7 (High vs Low)	**2.499**	**1.166–5.356**	**0.0185***	**2.011**	**1.036–3.906**	**0.03903***
Postoperative complications(≥ Grade II)	**0.703**	**0.390–1.266**	**0.2401**	**0.791**	**0.462–1.355**	**0.3933**

***S**tatistically significant

* *ESCC* Esophageal squamous cell carcinoma

minimalize postoperative complications, or minimalize postoperative CRP 7 d in the presence of complications, may improve the prognosis of esophageal cancer patients.

Abbreviations

ESCC	Esophageal squamous cell carcinoma
OS	Overall survival
RFS	Recurrence free survival
AUC	Area under the curve
PODs	Postoperative days

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Authors' contributions
YF and SE: Statistical analysis and wrote Introduction, Methods, Results and Discussion. MH and HK: Assisted data collections and clinical practice. Figure and Table formation. KY: assisted statistical analysis and comprehensive check. TU: Final check of manuscript and suggested appropriate corrections. All authors have read and approved the manuscript for submission.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available because permission from our hospital and university was not given, but are available from the corresponding author on reasonable request.

Data availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions in our hospital or university.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by The Research Ethics Committee(REC) of Kawasaki Medical School, approval number [5603–03]." Informed consent: Informed consent was obtained from all individual participants included in the study, and it was obtained in writing prior to surgery.

Consent for publication
No consent for publication.

Competing interests
The authors declare no competing interests.

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