Relationship Between Postoperative CRP and Prognosis in Thoracic Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim:* Few studies have examined postoperative CRP in esophageal cancer. We investigated the relationship between postoperative CRP values according to the postoperative period and prognosis in esophageal cancer. *Patients and Methods:* We performed a retrospective cohort study including 187 patients who underwent esophagectomy for esophageal squamous cell carcinoma (ESCC) between January 2008 and October 2016. *Results:* CRP within 1 month of surgery was not related to overall survival (OS) or recurrence-free survival (RFS). In a univariate analysis, postoperative 2 months (2M)-CRP ≥ 0.15 ml/dl was associated with poorer OS (41.4 vs. 71.4%, $p=0.0002$) and RFS (28.9 vs. 51.3%, $p=0.007$). In a multivariate analysis, 2M-CRP ≥ 0.15 ml/dl was an independent factor for poorer OS (HR=2.27, 95%CI=1.03-3.34, $p=0.005$) and RFS (HR=1.65, 95%CI=1.08-2.52, $p=0.020$). The incidence of postoperative pneumonia was significantly higher in the 2M-CRP ≥ 0.15 ml/dl group ($p=0.026$). *Conclusion:* 2M-CRP ≥ 0.15 ml/dl is an independent prognostic factor for ESCC. Furthermore, postoperative pneumonia may be associated with patient prognosis after esophagectomy.

Esophageal cancer is the eighth most common cancer worldwide, and the sixth most common cause of death from cancer (1). Multimodal therapy and perioperative management have recently improved; however, the prognosis of patients with esophageal cancer remains poor (2). A relationship has been reported between inflammation and malignant tumors. C-reactive protein (CRP) is the most common biomarker of

inflammation. Previous studies demonstrated that preoperative serum CRP was a prognostic factor for various types of cancers, such as colorectal cancer (3), esophageal cancer (4), and urological cancer (5). Some studies also examined postoperative CRP within 1 month of surgery for esophageal cancer (6, 7) and other cancers (8, 9). However, there is currently no information on CRP levels 2 months after surgery.

Postoperative complications may induce postoperative inflammation. The relationship between postoperative complications and patient prognosis has been investigated for various types of cancers (10, 11). However, the relationship between postoperative complications and patient prognosis in esophageal cancer remains controversial. In the present study, we investigated the relationships between postoperative CRP up to 2 months postoperatively, postoperative complications, and patient prognosis in ESCC.

Patients and Methods

Patients. We performed a retrospective cohort study including 187 patients who underwent esophagectomy for thoracic ESCC between January 2008 and October 2016 at our institution, for whom CRP values from the perioperative period to 2 months after surgery were noted. We excluded patients who received radiation therapy before surgery and patients with non-curative resected tumors. We selected a postoperative observation period of up to 5 years.

We evaluated superficial incisional surgical site infections (SSI), pneumonia, anastomotic leakage, and recurrent nerve paralysis as postoperative complications. All histopathological diagnoses were performed by experienced pathologists. T, N, and M categories and pathological stages were classified according to the pTNM Pathological Classification (UICC International Union Against Cancer TNM Classification of Malignant Tumors; 8th edition) (12).

CRP value measurements. Serum CRP levels were measured on postoperative days (PODs) 1, 3, 5, 7, and 14 and postoperative 1 month (1M) and 2 months (2M). According to our institution's standard, we set the cut-off value for 1M-CRP and 2M-CRP at 0.15 mg/dl. Since CRP elevations in most patients were confirmed within 14 days of surgery, we defined Max-CRP as the maximum CRP value on PODs 1, 3, 5, 7, and 14. The cut-off value for Max-CRP was set as 20 mg/dl.

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Key Words: Postoperative CRP, esophageal cancer.

Table I. Patient characteristics and CRP after surgery.

Variable	n	Max-CRP		p-Value	1M-CRP		p-Value	2M-CRP		p-Value
		<20 (n=120)	≥20 (n=67)		<0.15 (n=47)	≥0.15 (n=140)		<0.15 (n=101)	≥0.15 (n=86)	
Age										
<70	114	74	40	0.876	33	81	0.167	77	37	<0.0001*
≥70	73	46	27		14	59		24	49	
Gender										
Male	151	92	59	0.081	35	116	0.208	73	78	0.002*
Female	36	28	8		12	24		28	8	
BMI (kg/m ²)										
<22	112	85	27	<0.0001*	31	81	0.391	60	52	1.000
≥22	75	35	40		16	59		41	34	
HbA1c (%)										
<6.2	157	104	53	0.215	39	118	0.819	86	71	0.690
≥6.2	30	16	14		8	22		15	15	
Tumor location										
Ut	29	15	14	0.144	4	25	0.164	13	16	0.315
Mt/Lt	158	105	53		43	115		88	70	
Surgical time (min)										
<360	77	60	17	0.001*	25	52	0.061	35	42	0.054
≥360	110	60	50		22	88		66	44	
Blood loss (ml)										
<300	97	76	21	<0.0001*	32	65	0.012*	53	44	0.884
≥300	90	44	46		15	75		48	42	
pT										
pT1	75	42	33	0.063	17	58	0.607	42	33	0.765
pT2-3	112	78	34		30	82		59	53	
pN										
pN0	78	47	31	0.358	19	59	0.866	47	31	0.181
pN1-3	109	73	36		28	81		54	55	

BMI: Body mass index; Ut: upper esophagus; Mt: middle thoracic esophagus; Lt: lower esophagus; pT: pathological T stage; pN: pathological N stage. * $p < 0.05$: Fisher's exact test.

Statistical analysis. Data in our computerized database were examined in this retrospective study. Additional data were obtained by reviewing medical records. All analyses were performed using JMP software (version 12, SAS Institute Inc., Cary, NC, USA). Data were compared using Fisher's exact test to evaluate differences between qualitative variables. Survival curves were generated by the Kaplan–Meier method, and comparisons between groups were analyzed using the Log-rank test. A multivariate analysis was performed using Cox's proportional hazards model. A p -value of less than 0.05 was considered to be significant.

Results

Patient characteristics and CRP after surgery. We showed the characteristics of 187 patients, and compared clinical parameters between the high and low CRP groups in each period (Table I). Sixty-seven out of 187 (35.8%) patients were classified into the Max-CRP ≥ 20 mg/dl group, 140 (74.9%) into the 1M-CRP ≥ 0.15 mg/dl group, and 86 (46.0%) into the 2M-CRP ≥ 0.15 mg/dl. No significant

differences were observed in age, HbA1c, tumor location, or pN in each period between the high and low CRP groups. The Max-CRP ≥ 20 mg/dl group had a significantly higher proportion of BMI ≥ 22 , surgical time ≥ 360 min, and blood loss ≥ 300 ml. Furthermore, there were significantly more patients with 1M-CRP ≥ 0.15 mg/dl in the blood loss ≥ 300 ml group, and also significantly more patients with 2M-CRP ≥ 0.15 mg/dl in the age ≥ 70 years group.

Prognosis after surgery. We compared OS and RFS with each clinicopathological factor (Tables II and III). 2M-CRP ≥ 0.15 ml/dl was associated with poorer OS (41.4 vs. 71.4%, $p=0.0002$) and RFS (28.9 vs. 51.3%, $p=0.007$). In the multivariate analysis, 2M-CRP ≥ 0.15 ml/dl was an independent factor for poorer OS (HR=2.27, 95%CI=1.03-3.34, $p=0.005$) and RFS (HR=1.65, 95%CI=1.08-2.52, $p=0.020$). We made survival curves using the Kaplan–Meier method (Figure 1), which showed that the 2M-CRP ≥ 0.15 mg/dl group had poor OS and RFS in each period.

Table II. Overall survival rates.

Variable	Total n	OS (%)	Univariate analysis <i>p</i> -Value	Multivariate analysis		
				HR	95%CI	<i>p</i> -Value
Age						
<70	114	66.4%	0.024*	1.33	0.75-2.35	0.328
≥70	73	45.3%				
Gender						
Male	151	58.0%	1.000			
Female	36	62.0%				
BMI						
<22	112	57.5%	0.844			
≥22	75	62.2%				
HbA1c (%)						
<6.2	157	61.9%	0.204			
≥6.2	30	42.1%				
Tumor location						
Ut	29	79.9%	0.065			
Mt/Lt	158	55.8%				
Surgical time (min)						
<360	77	56.9%	0.424			
≥360	110	60.5%				
Blood loss (ml)						
<300	97	61.8%	0.888			
≥300	90	57.0%				
pT						
pT1	75	67.9%	0.022*	1.81	1.04-3.33	0.037**
pT2-3	112	53.5%				
pN						
pN0	78	71.4%	0.018*	1.81	1.03-3.34	0.040**
pN1-3	109	51.0%				
Preoperative CRP (mg/dl)						
<0.15	121	58.6%	0.936			
≥0.15	66	60.5%				
Max-CRP (mg/dl)						
<20	120	57.5%	0.529			
≥20	67	61.4%				
1M-CRP (mg/dl)						
<0.15	47	68.6%	0.173			
≥0.15	140	55.5%				
2M-CRP (mg/dl)						
<0.15	101	71.4%	0.0002*	2.27	1.03-3.34	0.005**
≥0.15	86	41.4%				

BMI: Body mass index; Ut: upper esophagus; Mt: middle thoracic esophagus; Lt: lower esophagus; pT: pathological T stage; pN: pathological N stage. * $p<0.05$; Log-rank test; ** $p<0.05$: Cox's hazard regression analysis.

CRP after surgery and postoperative complications. Postoperative complications between the 2M-CRP <0.15 mg/dl group and ≥0.15 mg/dl group were compared (Table IV). No significant differences were observed in S-SSI, anastomotic leakage, or recurrent nerve paralysis between the two groups. However, the incidence of pneumonia was significantly higher in the 2M-CRP ≥0.15 mg/dl group.

Discussion

CRP is a blood test marker for inflammation in the body, and is produced in the liver. CRP is classified as an acute phase

reactant and increases in response to inflammation. CRP plays a key role in host defenses against infection and was given its name because it reacts with the C-polysaccharide of *Streptococcus pneumoniae* (13). This is the first study to investigate the relationship between CRP 2 months after surgery and patient prognosis. In the present study, 2M-CRP ≥0.15 mg/dl was associated with significantly poorer OS and RFS. Ibuki *et al.* previously reported that 7PODs-CRP and 1M-CRP were associated with poor RFS (6). Matsuda *et al.* showed that an intense postoperative inflammatory response (CRP within 14 days of surgery) was an independent risk factor for poor OS and RFS (7). In this study, CRP within 1 month

Table III. Recurrence-free survival rates.

	Total n	RFS (%)	Univariate analysis <i>p</i> -Value	Multivariate analysis		
				HR	95%CI	<i>p</i> -Value
Age						
<70	114	46.7%	0.304			
≥70	73	30.8%				
Gender						
Male	151	41.4%	0.958			
Female	36	42.9%				
BMI						
<22	112	37.8%	0.483			
≥22	75	51.4%				
HbA1c (%)						
<6.2	157	40.4%	0.661			
≥6.2	30	51.6%				
Tumor location						
Ut	29	58.7%	0.141			
Mt/Lt	158	39.1%				
Surgical time (min)						
<360	77	34.8%	0.110			
≥360	110	46.8%				
Blood loss (ml)						
<300	97	33.4%	0.230			
≥300	90	48.8%				
pT						
pT1	75	65.7%	<0.0001*	2.87	1.77-4.85	<0.0001**
pT2-3	112	27.6%				
pN						
pN0	78	52.5%	0.0009*	1.89	1.21-3.05	0.005**
pN1-3	109	34.3%				
Preoperative CRP (mg/dl)						
<0.15	121	45.2%	0.772			
≥0.15	66	37.3%				
Max-CRP (mg/dl)						
<20	120	40.0%	0.294			
≥20	67	45.5%				
1M-CRP (mg/dl)						
<0.15	47	53.1%	0.262			
≥0.15	140	37.3%				
2M-CRP (mg/dl)						
<0.15	101	51.3%	0.007*	1.65	1.08-2.52	0.020**
≥0.15	86	28.9%				

BMI: Body mass index; Ut: upper esophagus; Mt: middle thoracic esophagus; Lt: lower esophagus; pT: pathological T stage; pN: pathological N stage. **p*<0.05: Log-rank test; ***p*<0.05: Cox's hazard regression analysis.

was not associated with patient prognosis. On the other hand, 2M-CRP ≥0.15 mg/dl was associated with significantly poorer OS and RFS. These results indicate that chronic rather than acute inflammation is associated with enhanced cancer growth. Although it is widely known that chronic inflammation is involved in carcinogenesis, for example, hepatic cell carcinoma, gastric cancer, and cervical cancer (14), few studies have investigated its relationship with cancer growth. Petrzyk *et al.* reported that obesity-related chronic inflammation induced cancer cell proliferation, invasion, and metastasis *via* the activation of several signal transduction pathways (JAK/STAT,

mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase (PI3K), and mTOR) in colorectal cancer (15).

In the present study, the incidence of pneumonia was significantly higher in the 2M-CRP ≥0.15 mg/dl group. On the other hand, Max-CRP ≥20 mg/dl and 1M-CRP ≥0.15 mg/dl were not associated with the occurrence of pneumonia. This has been attributed to postoperative pneumonia after esophagectomy occurring at various times after surgery. Previous studies also reported that postoperative pneumonia was associated with a poor prognosis in patients with esophageal cancer (16, 17). These findings suggest the

Figure 1. Survival curves of patients after curative resection for ESCC according to postoperative CRP levels. OS (upper panel) and RFS (lower panel) were poor in the 2M-CRP ≥ 0.15 mg/dl group in each period. * $p < 0.05$: Log-rank test.

importance of minimally invasive esophagectomy, which may decrease the incidence of postoperative respiratory complications, from an oncological point of view (18-20).

There is also evidence to indicate that tumor growth increases CRP (21); however, it currently remains unclear whether elevated CRP is the cause or result of cancer growth. In the present study on patients with curative resected tumors, there were no relationships between postoperative CRP values and oncological factors, such as pT and pN, suggesting that

our results on CRP were mainly influenced by inflammatory rather than oncological factors. In conclusion, 2M-CRP ≥ 0.15 ml/dl was identified as an independent prognostic factor for ESCC. Furthermore, postoperative pneumonia may be associated with patient prognosis after esophagectomy.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

Table IV. CRP after surgery and postoperative complications.

Complication	Total n	2M-CRP		*p-Value
		<0.15 (n=101)	≥0.15 (n=86)	
S-SSI				
Present	12	8	4	0.551
Absent	175	93	82	
Pneumonia				
Present	29	10	19	0.026*
Absent	158	91	67	
Anastomotic leakage				
Present	27	12	15	0.303
Absent	160	89	71	
Recurrent nerve paralysis				
Present	76	39	37	0.554
Absent	111	62	49	

S-SSI: Superficial incisional surgical site infection. * $p < 0.05$: Fisher's exact test.

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