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Original article

C-reactive Protein to Albumin Ratio is a Prognostic Factor for Patients with cStage II/III

Esophageal Squamous Cell Cancer

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Abstract

C-reactive protein to albumin (CRP/Alb) ratio, a novel inflammation-based prognostic score, was first developed as a prognostic score for septic patients. Recent reports show that CRP/Alb ratio is also a prognostic score for cancer patients, including esophageal cancer. However, the role of CRP/Alb ratio for those with neoadjuvant chemotherapy (NAC) and the changes of CRP/Alb ratio around NAC has never been discussed. The aim of this study was to evaluate the significance of CRP/Alb ratio around NAC for patients with cStage II/III esophageal squamous cell cancer (ESCC). A total of 149 patients who were diagnosed as cStage II/III ESCC were enrolled between February 2007 to December 2014. We retrospectively investigated the relation between Pre-NAC and Post-NAC CRP/Alb ratio and short and long outcomes. The optimal cut-off level for Pre-NAC and Post-NAC CRP/Alb ratio was 0.030 and 0.048, respectively. There was no relation between CRP/Alb ratio level and postoperative outcomes. Post-NAC CRP/Alb ratio < 0.048 had a significantly higher overall survival rate than CRP/Alb ratio $\geq$ 0.048 ($P < 0.001$). Univaritae analysis showed that cT, cN, Pre-NAC CRP/Alb ratio < 0.030 and Post-NAC CRP/Alb ratio < 0.048 was prognostic factors ($P = 0.003$, $P = 0.022$, $P = 0.033$ and $P < 0.001$, respectively). Multivariate analysis showed that cT and Post-NAC CRP/Alb ratio <0.048 was independent prognostic factors ($P = 0.030$ and $P < 0.001$, respectively). Post-NAC CRP/Alb ratio is an independent prognostic factor in patients with

cStage II/III ESCC.

Key Words

C-reactive protein, Albumin, mGPS, Esophageal cancers, Neoadjuvant chemotherapy

Introduction

Despite of the advances in preoperative diagnosis and surgical techniques, esophageal cancer is one of the most lethal malignancies with low 5-year survival rate [1]. In Japan, most of the esophageal cancers are squamous cells [2], and neoadjuvant chemotherapy (NAC) followed by operation is standard treatment for cStage II/ III esophageal squamous cell cancer (ESCC) [3].

C-reactive protein (CRP) and albumin which is well known acute phase proteins, correlate with long-term outcomes in ESCC patients [4-8]. Modified Glasgow prognostic score (mGPS) is a simple classification that consists of CRP and albumin. We previously showed that mGPS changes after NAC and Post-NAC mGPS is a prognostic factor [5]. Recent study showed that CRP to albumin (CRP/Alb) ratio reflects prognosis better than mGPS, since CRP/Alb ratio is a continuous variable [6, 7]. However, it is not clear whether CRP/Alb ratio is still effective for patients after NAC. In this study, we retrospectively invested CRP/Alb ratio to evaluate the prognostic value for patients with ESCC after NAC.

Patients and Methods

Study population

Patients who were diagnosed as cStage II/III squamous cell esophageal cancer at Kobe University Hospital during February 2007 to December 2014, were investigated to the study. cStage was assessed based on esophagogastroduodenoscopy (EGD) and computed tomography (CT) before treatment and TNM classification was determined according to the 6th edition of Unio Internationalis Contra Cancrum Classification [9]. All patients enrolled into this study had NAC and indication for curative surgery according to the preoperative examination by EGD and enhanced chest and abdominal CT scan. Clinical follow-up data were observed by retrospectively studying the patient clinical charts. All study participants provided informed consent, and the study design was approved by the ethics review board at Kobe University Hospital and conforms to the provisions of the 1995 Declaration of Helsinki.

Neoadjuvant Chemotherapy

The NAC regimen consisted of cisplatin plus 5-fluorouracil repeated twice every 3 weeks. Cisplatin was administered at a dose of 80 mg/m^2 by intravenous drip infusion for 2 hours on day 1, and 5-fluorouracil was administered at a dose of 800 mg/m^2 by continuous intravenous infusion on days 1–5 [3]. In general, 2 course of chemotherapy is performed before operation. However, in cases with tumor progression after 1 course of chemotherapy or strong side-effects due to chemotherapy, only 1course is performed before operation.

Statistical analysis.

The difference between 2 groups was analyzed by using the Chi-square test, and

Student's T test or Mann-Whitney U test. The optimal cut-off level of the CRP/Alb ratio was

determined by a receiver operating characteristics (ROC) analysis. The Survival time was

calculated from the first visited date to our hospital to the occurrence of the event or the last

known date of follow-up. Survival analysis was performed using the Kaplan–Meier method

with the log-rank test. Variables with a P value < 0.2 in a univariate analysis were further

evaluated in a multivariate analysis using the Cox proportional hazard model to assess the

predictors for survival. In all analyses, a $P < 0.05$ was accepted as statistically significant.

Descriptive statistics were obtained using the JMP statistical software package (JMP® 11, SAS

Institute Inc., Cary, NC, USA).

Results

The characters of patients who were invested in this study are listed in Table 1. One

hundred forty-nine patients were enrolled to this study. The mean age is 66.9±8.3 years, most

patients were male, and the main tumor was located in the middle thoracic. The majority of

tumor depth was deeper than T3, and lymphatic metastasis positive, and cStage III. The

Pre-NAC CRP was higher and Pre-NAC albumin was lower than those of Post-NAC CRP and albumin. The patients of mGPS 0 increased from 128 to 136 patients after NAC.

Applying ROC analysis to the survival status, the optimal cut-off level for the Pre-NAC CRP/Alb was 0.030, with the area under the curve (AUC) was 0.589, and the cut-off level for the Post-NAC CRP/Alb was 0.048, with the AUC 0.703.

The surgical outcomes and postoperative complications are listed in Table2. There was no relation between Post-NAC CRP/Alb ratio level and operation time or blood loss. There were no differences in anastomotic leakage, lung complications, or in-hospital death according to the Post-NAC CRP/Alb ratio level.

The 5–year survival of all patients was 55.5%. Sixty-one patients died during the observation. Forty-nine patients died of progression of the esophageal cancer. Four patients died of other cancers. Six patients died of non-cancer death. Two patients died of operation related death. The recurrence was observed in 83 patients. The most observed recurrence site was the lymph node (51.8%) followed by other organs (36.1%) and local site (3.6%).

Patients were classified into 2 groups according to the CRP/Alb cut-off level 0.030 for Pre-NAC and 0.048 for Post-NAC. There was significant difference in overall survival between

Pre-NAC CRP/Alb level ($P = 0.046$, Fig. 1A) and Post-NAC CRP/ Alb level ($P < 0.001$, Fig. 1B). Univariate and multivariate analyses were performed to indicate the prognostic factor of cStage II/III ESCC (Table 3). In univariate analysis, cT, cN, Pre-NAC CRP/Alb ratio < 0.030 and Post-NAC CRP/Alb ratio < 0.048 was shown as prognostic factors ($P = 0.003$, $P = 0.022$, $P = 0.033$, and $P < 0.001$, respectively). In multivariate analysis, cT and Post-NAC CRP/Alb ratio <0.048 was shown as independent prognostic factor ($P = 0.030$ and $P < 0.001$, respectively).

Discussions

The preoperative systematic response such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, and prognostic nutritional index are also known as prognostic scores for esophageal cancer [10, 11]. Previous study showed that CRP/Alb ratio was better associated with overall survival than other prognostic scores [6]. Our previous study showed that inflammatory and nutrition status changes around NAC, and Post-NAC mGPS is a prognostic factor [5]. However, most patients were classified as mGPS 0 and could not predict poor prognosis cases in that group. So in this study, we investigated prognostic scores that use CRP and albumin and found that Post-NAC CRP/Alb ratio is an independent prognostic factor for ESCC. This might be because CRP/Alb is a continuous variable. We calculated both cut-off level of CRP/Alb before and after NAC, and found that CRP/Alb level

after NAC had a higher AUC than that of before NAC. This is because Post-NAC CRP was significantly lower and albumin was higher than Pre-NAC CRP and albumin ($P = 0.020$ and $P = 0.178$, respectively).

Post-NAC CRP/Alb ratio was a prognostic factor, while Pre-NAC CRP/Alb ratio was not. This might be explained by two reasons. First, high histological response after NAC is known to have a better survival than low histological response [12]. In our study, CRP/Alb ratio improved in 84 patients (56.4 %) and high histological response was more observed in those with Post-NAC CRP/Alb ratio using 0.048 as a cut-off level while Pre-NAC CRP/Alb ratio using 0.030 as a cut-off level did not have any difference (data not shown). These suggest that Post-NAC CRP/Alb ratio reflects the response of NAC better than Pre-NAC CRP/Alb ratio. Second is because cancer progression was suppressed and food intake improved after NAC. CRP is a prototype protein that is produced within a few hours by the liver in response to inflammatory cytokines [13]. Elevated CRP in patients with malignancy is mostly likely a response to secondary tumor necrosis and local tissue damage [14]. On the other hand, albumin is one of the most commonly used indicators of nutritional status [15]. Low albumin is often observed in patients with chronic disease and advanced cancer, which is associated with poor prognosis [16, 17]. There is a study showing that albumin level improved after chemotherapy due to resumption of adequate oral nutrition [18]. Thus, low

CRP/Alb ratio represents good general status. Since preoperative immunonutrition is

reported to suppress the perioperative inflammatory response and leads to

postoperative complications [18], it might also help to improve the survival.

There are a few limitations to this study. CRP is not a specific marker of inflammation,

and it could be influenced by other systematic diseases. We were not able to show the relation

between Post-NAC CRP/Alb ratio level and postoperative outcomes. This is retrospective study

conducted by single institution. Cut-off level of CRP/Alb ratio was determined from the data of

our institution. So the cut-off level differs in reports that range between 0.050-0.095 [6, 7].

In conclusion Post-NAC CRP/Alb ratio is in independent prognostic factor for cStage

II/III ESCC. To determine the standard cut-off level of CRP/Alb, it should be further evaluated

in larger prospective studies.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.

2. Tachimori Y, Ozawa S, Numasaki H, et al. Comprehensive Registry of Esophageal Cancer in Japan, 2009 Esophagus 2016; 13:110-37.

3. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.

4. Matsuda S, Niihara M, Tsubosa Y, et al. Clinical significance of postoperative recovery of serum albumin levels in patients with esophageal cancer who underwent transthoracic esophagectomy. Surg Today 2016.

5. Otowa Y, Nakamura T, Takiguchi G, et al. Changes in modified Glasgow prognostic score after neoadjuvant chemotherapy is a prognostic factor in clinical stage II/III esophageal cancer. Dis Esophagus 2016;29:146-51.

6. Xu XL, Yu HQ, Hu W, Song Q and Mao WM. A Novel Inflammation-Based Prognostic Score, the C-Reactive Protein/Albumin Ratio Predicts the Prognosis of Patients with Operable Esophageal Squamous Cell Carcinoma. PLoS One 2015;10:e0138657.

7. Wei XL, Wang FH, Zhang DS, et al. A novel inflammation-based prognostic score in

esophageal squamous cell carcinoma: the C-reactive protein/albumin ratio. BMC Cancer 2015;15:350.

8. Hirahara N, Matsubara T, Hayashi H, et al. Impact of inflammation-based prognostic score on survival after curative thoracoscopic esophagectomy for esophageal cancer. Eur J Surg Oncol 2015;41:1308-15

9. Sobin L H, Wittekind C. TNM Classification of Malignant Tumors. 6th edn. New York: Wiley-Liss; 2002, p. 60–5.

10. Hyder J, Boggs DH, Hanna A, Suntharalingam M and Chuong MD. Changes in neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios during chemoradiation predict for survival and pathologic complete response in trimodality esophageal cancer patients. J Gastrointest Oncol 2016;7:189-95.

11. Nozoe T, Kimura Y, Ishida M, et al. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. Eur J Surg Oncol 2002;28:396-400.

12. Konishi H, Fujiwara H, Shiozaki A, et al. Effects of netropenia and histological responses in esophageal squamous cell carcinomoa with neo-adjuvant chemotherapy. Int J Clin Oncol 2016;21:95-101.

13. Castell JV, Gomez-Lechon MJ, David M, et al. Acute-phase response of human

hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. Hepatology 1990;12:1179-86.

14. Wang CS and Sun CF. C-reactive protein and malignancy: clinico-pathological association and therapeutic implication. Chang Gung Med J 2009;32:471-82.

15. Gupta D and Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010;9:69.

16. Lindenmann J, Fink-Neuboeck N, Koesslbacher M, et al. The influence of elevated levels of C-reactive protein and hypoalbuminemia on survival in patients with advanced inoperable esophageal cancer undergoing palliative treatment. J Surg Oncol 2014;110:645-50.

17. Yokota T, Ando N, Igaki H, et al. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology 2015;89:143-51.

18. Cools-Lartigue J, Jones D, Spicer J, et al. Management of Dysphagia in Esophageal Adenocarcinoma Patients Undergoing Neoadjuvant Chemotherapy: Can Invasive Tube Feeding be Avoided? Ann Surg Oncol 2015;22:1858-65.

19. Giger U, Buchler M, Farhadi J, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a

randomized controlled pilot study. Ann Surg Oncol 2007;14:2798-806.

Figure Legends

Figure 1.

(A) Pre-NAC CRP/Alb < 0.030 had a higher overall survival rate than Pre-NAC CRP/Alb ≥

0.030. (B) Post-NAC CRP/Alb < 0.048 had a higher overall survival rate than Post-NAC

CRP/Alb ≥ 0.048.

Table 1. Characteristics of patients who had NAC followed by surgery.

Variables	Patients (n = 149)
Age, mean±S.D. (years)	66.9±8.3
Sex	
Male/ Female	129/20
Tumour Site	
Ut/Mt/Lt	24/73/52
cT	
1/2/3/4	22/28/98/1
cN	
+/-	125/24
cStage	
IIA/IIB/III	24/36/89
Pre-NAC CRP, median (range) (mg/dl)	0.14 (0.03-5.9)
Post-NAC CRP, median (range) (mg/dl)	0.11 (0.03-6.1)
Pre-NAC albumin, median (range) (g/dl)	3.8 (2.5-4.8)
Post-NAC albumin, median (range) (g/dl)	3.9 (2.3-4.9)

Pre-NAC mGPS	
0/1/2	128/9/12
Post-NAC mGPS	
0/1/2	136/13/10

NAC, neoadjuvant chemotherapy; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic;

CRP, C-reactive protein; mGPS, modified Glasgow Prognostic Score

Table 2. Surgical outcomes and postoperative complications.

	Post-NAC CRP/Alb ratio		
	<0.048	0.048≤	
Variables	(n=102)	(n=47)	*P* value
Surgical outcomes			
Operation time, median (range) (min)	679 (419-1361)	724 (446-1106)	0.190
Blood loss, median (range) (ml)	408 (60-2605)	420 (30-1342)	0.851
Postoperative complications			
Anastomotic leakage	12 (11.8%)	7 (14.9%)	0.599
Pulmonary complication	29 (28.4%)	13 (27.7%)	0.922
In-hospital death	1 (1.0%)	1 (2.1%)	0.533

NAC, neoadjuvant chemotherapyCRP, C-reactive protein; Alb, albumin

Table 3. Results of analysis of overall survival.

Variables	Patients (n = 149)	Univariate analysis HR (95 % CI)	P value	Multivariate analysis HR (95 % CI)	P value
Age, years		0.882			
(<70/70≤)	84/65	(0.533-1.469)	0.626		
Sex (Male/		1.248			
Female)	129/20	(0.628-2.843)	0.549		
Tumour Site		1.312			
(Ut/ Mt,Lt)	24/125	(0.682-2.348)	0.398		
cT (1,2/ 3,4)		0.411		0.512	
	50/99	(0.209-0.747)	0.003	(0.258-0.939)	0.030
cN (+/-)		2.562		1.759	
	125/24	(1.133-7.349)	0.022	(0.765-5.101)	0.200
Pre-NAC CRP/					
Alb		0.477		0.868	
(<0.030/≤0.030)	35/114	(0.209-0.946)	0.033	(0.371-1.781)	0.715
Post-NAC CRP/	102/47	0.257	<0.001	0.298	<0.001

Alb	(0.153-0.428)	(0.174-0.503)
(<0.048/≤0.048)		

HR, hazard ratio; CI, confidence interval; NAC, neoadjuvant chemotherapy; Ut, upper thoracic;

Mt, middle thoracic; Lt, lower thoracic; CRP, C-reactive protein; Alb, albumin

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Pre-NAC mGPS	

0/1/2	128/9/12
Post-NAC mGPS	
0/1/2	136/13/10

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Tumour Site (Ut/ Mt,Lt)	24/125	1.312 (0.682-2.348)	0.398		
cT (1,2/ 3,4)	50/99	0.411 (0.209-0.747)	0.003	0.512 (0.258-0.939)	0.030
cN (+/-)	125/24	2.562 (1.133-7.349)	0.022	1.759 (0.765-5.101)	0.200
Pre-NAC CRP/Alb (<0.030/ 0.030≤)	35/114	0.477 (0.209-0.946)	0.033	0.868 (0.371-1.781)	0.715
Post-NAC CRP/Alb (<0.048/ 0.048≤)	102/47	0.257 (0.153-0.428)	<0.001	0.298 (0.174-0.503)	<0.001

HR, hazard ratio; CI, confidence interval; NAC, neoadjuvant chemotherapy; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; CRP,

C-reactive protein; Alb, albumin