ANTICANCER RESEARCH *36*: 6557-6562 (2016)
doi:10.21873/anticanres.11259

Prognostic Significance of Inflammatory and Nutritional Parameters in Patients with Esophageal Cancer

TATSUYA MIYAZAKI[1], MAKOTO SAKAI[1], MAKOTO SOHDA[1], NARITAKA TANAKA[1], TAKEHIKO YOKOBORI[2], YOKO MOTEGI[3], MASANOBU NAKAJIMA[4], MINORU FUKUCHI[5], HIROYUKI KATO[4] and HIROYUKI KUWANO[1]

Departments of [1]General Surgical Science, [2]Molecular Pharmacology and Oncology, and [3]Thoracic Visceral Organ Surgery, Gunma University Graduate School of Medicine, Gunma University, Gunma, Japan;
[4]First Department of Surgery, Dokkyo Medical University, Tochigi, Japan;
[5]Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Abstract. *Background: We evaluated the following preoperative prognostic factors in patients who underwent esophagectomy for esophageal cancer: C-Reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), serum albumin, prognostic nutritional index (PNI), and body mass index (BMI). Patients and Methods: This retrospective study included 173 men and 19 women with a mean age of 65.8 years (range=42-86 years) who were scheduled to undergo esophagectomy for esophageal cancer. The association of CRP, NLR, albumin, PNI, and BMI with various clinicopathological factors and prognosis were evaluated. Results: Univariate analysis revealed that male sex, depth of invasion, nodal metastasis, pStage, high CRP, low PNI, high NLR, and low BMI were significant risk factors for a poor prognosis. Multivariate analysis identified depth of invasion, pStage, and BMI as significant prognostic factors in the Cox proportional hazard model. Conclusion: The preoperative nutritional status affected the postoperative survival time in patients with esophageal cancer. In particular, a low BMI was an independent prognostic factor for poorer survival in the multivariate analysis.*

An increasing number of esophageal carcinomas are diagnosed worldwide each year (1). The prognosis is poor, and the overall 5-year survival rate for patients with esophageal squamous cell carcinoma ranges from 15% to 25% (2).

The preoperative nutritional status is a very important factor in esophageal cancer treatment because patients cannot take in enough food due to local stenosis and become cachexic with advanced esophageal carcinoma. Some studies have described benchmarks for nutrition-related prognostic factors (3 ,4). The serum albumin concentration, body mass index (BMI), and prognostic nutritional index (PNI) are reportedly related to postoperative complications and prognosis (4-6). Additionally, the body's inflammatory response plays an important role in tumor occurrence and development, and is therefore another prognostic factor (7, 8). C-Reactive protein (CRP) is the most commonly used measure of systemic inflammation in clinical practice, and it has been shown to be an independent predictor of survival in patients undergoing surgical resection for several types of cancers (9, 10). The neutrophil-to-lymphocyte ratio (NLR) is also a reported prognostic factor that indicates inflammation immune response to several types of cancers (11, 12). However, there is no consensus about the relationship between these factors and a patient's prognosis. Additionally, which is the most clinically valuable factor remains unknown. Therefore, we evaluated the following preoperative prognostic factors for patients with esophageal cancer who underwent esophagectomy: CRP, albumin, PNI, NLR, and BMI.

Materials and Methods

Patients. This retrospective study included 173 men and 19 women with a mean age of 65.8 years (range=42-86 years) who were scheduled to undergo esophagectomy for treatment of esophageal cancer from February 2004 to November 2014. All patients underwent R0 resection without preoperative adjuvant therapy.

Correspondence to: Tatsuya Miyazaki, MD, Ph.D., FACS, Department of General Surgical Science, Gunma University, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81 272208224, Fax: +81 272208230, e-mail: tatsuyamiyazaki@gunma-u.ac.jp

Key Words: Prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), body mass index (BMI).

Patients who were regarded as having malnutrition at the first visit received enteral nutrition at 375 to 1500 kcal/day *per os* until admission. This study was approved by the Institutional Review Board of our hospital, and all patients provided written informed consent before enrollment (approval number 1457). The tumor stage was classified according to the seventh edition of the TNM classification of the International Union against Cancer(13). The mean postoperative follow-up period for the 192 patients was 26.5 months (range=1-108 months).

Nutritional assessment. The preoperative blood cell count and biochemical examination data were retrospectively extracted from the medical records. Peripheral blood samples were gathered within 2 weeks before surgery. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and was categorized into two groups: ≤3.49 and >3.49.

BMI was calculated according to the standardized definition as weight in kilograms divided by height in meters squared(14). Weight and height were measured within 2 weeks prior to surgery.

The PNI was defined as follows: PNI=10 × albumin + 0.005 × absolute lymphocyte count(15).

We used a receiver-operating characteristic curve to determine the appropriate cutoff values for CRP, albumin, NLR, PNI, and BMI in the analysis of overall survival. We determined cutoff values for CRP, albumin, NLR, PNI, and BMI to be 0.18, 3.7, 3.49, 47.7 and 22.5 respectively.

Surgery. We performed surgery using one of two different techniques. Of the 192 patients, 141 underwent cervicothoracoabdominal three-field lymph node dissection through a right-sided thoracotomy (McKeown procedure). The remaining 51 patients underwent thoracoabdominal two-field dissection through a right-sided thoracotomy with reconstruction of the posterior mediastinal route (Ivor Lewis procedure). The latter patients were elected according to the indications for operations of our Department (16). Our indications for this procedure were a tumor located in the middle or lower thoracic esophagus and restricted to within the esophageal submucosal layer, and no evidence of neck lymphadenopathy nor any prominent intramediastinal lymph node swellings on preoperative examination.

Statistical analysis. Continuous variables are expressed as the mean±standard deviation. The associations of CRP, albumin, NLR, PNI, and BMI with clinicopathological factors were analyzed using Student's *t*-test, the chi-square test, and analysis of variance. Overall and cancer-specific survival were measured from the day of surgery and plotted according to the Kaplan–Meier method; the log-rank test was used for comparison. Cox proportional hazards regression was used to analyze univariate and multivariate prognostic factors. All statistical analyses were performed using the JMP software package (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at $p<0.05$.

Results

The clinicopathological characteristics of patients are shown in Table I. We identified a relationship between CRP and tumor location ($p<0.01$), T factor (depth of invasion) ($p<0.0001$), and pathological stage (pStage) ($p<0.05$). Patients in the low-albumin group were older than those in the high-albumin group ($p<0.05$). The low-albumin group contained no female patients. There was no relationship between NLR and age, sex, tumor location, or TNM stage. Patients with low PNI had deeper invasion of tumor than those with high PNI ($p<0.05$). There was no relationship between BMI and age, sex, tumor location, or TNM stage.

The results of the univariate and multivariate analyses of overall survival after esophagectomy in patients with esophageal cancer are shown in Table II. The univariate analysis revealed that male sex, depth of invasion (pT3, 4), nodal metastasis (positive), pStage (Stage 3, 4), low BMI, low PNI, high NLR, and high CRP were significant factors related to a poor prognosis (Table II; Figures 1 and 2). The multivariate analysis confirmed depth of invasion, pStage, and BMI to be independent prognostic factors in patients who underwent esophagectomy. Moreover, the high-BMI group had a better prognosis than the low-BMI group in terms of disease-specific survival ($p<0.01$) (Figure 2).

Discussion

In our study, patients with a lower BMI had a poorer prognosis than patients with a higher BMI. A low BMI was confirmed as an independent poor prognostic factor in the multivariable logistic regression analysis. Zhang *et al*. performed a meta-analysis of the relationship among complications, survival, and BMI. They showed that a higher BMI was associated with increased complications and that a high BMI could improve overall survival when they analyzed the prognosis in three groups(6). In our cohort, only two patients (1.0%) had a BMI of >30.0 kg/m^2, and 26 patients (13.5%) had a BMI of >25.0 kg/m^2. Therefore, we believe that it was difficult to evaluate the influence of obesity on the prognosis of our patients who underwent esophagectomy. In our study, the reason for the poor prognosis in patients with a lower BMI is thought to have been their lower nutrition status.

A low serum albumin concentration is associated with postoperative complications and prognosis (17). The preoperative serum albumin concentration was not a prognostic factor in our study. The preoperative serum albumin level may not adequately reflect the prognosis in patients with esophageal cancer.

The PNI was first suggested to be a nutritional index and a predictor of surgical risk by Buzby *et al*. in 1980 (18), and this was corroborated by Onodera *et al*. in 1984 (15). Numerous studies have recently shown that a low PNI is an independent adverse prognostic factor for short-term postoperative complications and long-term outcomes in many different types of cancer, including gastric, colorectal, and esophageal (19-21). Sun *et al*. reported that PNI might be an effective predictive indicator for digestive system carcinoma according to their meta-analysis of cancer arising

Table I. *Patient characteristics*.

Characteristic	Total (n=192)	CRP			Albumin≤3.7			NLR			PNI			BMI		
		CRP≤ 0.18 mg/dl (n=110)	CRP> 0.18 mg/dl (n=82)		albumin ≤3.7 g/dl (n=23)	albumin >3.7 g/dl (n=169)		NLR≤ 3.49 (n=150)	NLR> 3.49 (n=42)		PNI≤ 47.7 (n=65)	PNI> 47.7 (n=127)		BMI≤ 22.5 kg/m^2 (n=108)	BMI> 22.5 kg/m^2 (n=84)	
Age (years)																
mean (range)	66.0 (42-86)	65.3 (42-80)	66.9 (52-86)	0.1	70.2 (54-86)	65.4 (42-86)	<0.05	66.3 (42-86)	65.9 (49-80)	0.96	67.7 (45-86)	65.1 (42-81)	0.07	65.4 (49-86)	66.7 (42-86)	0.15
Gender																
Male	173	96	77	0.13	23	150	<0.05	132	41	0.07	60	113	0.46	97	76	0.88
Female	19	14	5		0	19		18	1		5	14		11	8	
Location										0.33			0.18			
Ut	17	11	6	<0.01	1	16	0.11	11	6		4	13		10	7	0.67
Mt	89	61	28		7	82		72	17		26	63		47	42	
Lt	86	38	48		15	71		67	19		35	51		51	35	
TNM clinical classification (7th)																
T																
T1	84	65	19	<0.0001	7	77	0.58	68	16	0.36	19	65	<0.05	46	38	0.15
T2	23	13	10		3	20		18	5		9	14		9	14	
T3	79	30	49		12	67		61	18		34	45		48	31	
T4	6	2	4		1	5		3	3		3	3		5	1	
N																
N0	80	51	29	0.1	11	69	0.92	63	17	0.15	26	54	0.76	43	37	0.91
N1	60	31	29		6	54		49	11		20	40		36	24	
N2	34	15	19		4	30		22	12		14	20		19	15	
N3	18	13	5		2	16		16	2		5	13		10	8	
M																
M0	170	98	72	0.78	22	148	0.25	134	36	0.52	58	112	0.83	97	73	0.53
M1	22	12	10		1	21		16	6		7	15		11	11	
pStage				<0.05			0.17			0.64			0.57			0.35
I	58	43	15		9	49		47	11		16	42		28	30	
II	50	28	22		3	47		41	9		17	33		31	19	
III	60	27	33		10	50		44	16		24	36		37	23	
IV	24	12	12		1	23		18	6		8	16		12	12	

Ut: Upper thoracic esophagus, Mt: middle thoracic esophagus, Lt: lower thoracic esophagus, CRP: c-reactive protein, NLR: neutrophil-to-lymphocyte ratio, PNI: prognostic nutritional index, BMI: body mass index.

Table II. *Univariate and multivaliate analyses of overall survival after esophagectomy.*

Characteristic	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age (years)	1.24	0.938-1.654	0.13			
Gender, male	2.43	1.128-10.137	0.0175	2.12	0.951-9.048	0.0704
pT3,4	2.14	1.565-3.023	<0.0001	1.45	1.006-2.178	0.0463
Nodal metastasis positive	1.44	1.070-2.003	0.0157	1.36	0.731-2.681	0.3367
pStage 3,4	1.92	1.426-2.643	<0.0001	1.99	1.042-4.049	0.0367
BMI (low)	1.53	1.127-2.139	0.0056	1.4	1.023-1.985	0.0353
PNI (low)	1.35	1.019-1.793	0.0366	1.0916	0.798-1.489	0.5803
NLR (high)	1.6	1.192-2.128	0.0022	1.2	0.849-1.676	0.2976
Albumin (low)	1.38	0.930-1.936	0.1039			
CRP (high)	1.67	1.251-2.285	0.0005	1.24	0.9082-1.740	0.176

BMI: Body mass index, PNI: prognostic nutritional index, NLR: neutrophil-to-lymphocyte ratio, CRP: c-reactive protein, OR: odds ratio, CI: confidence interval.

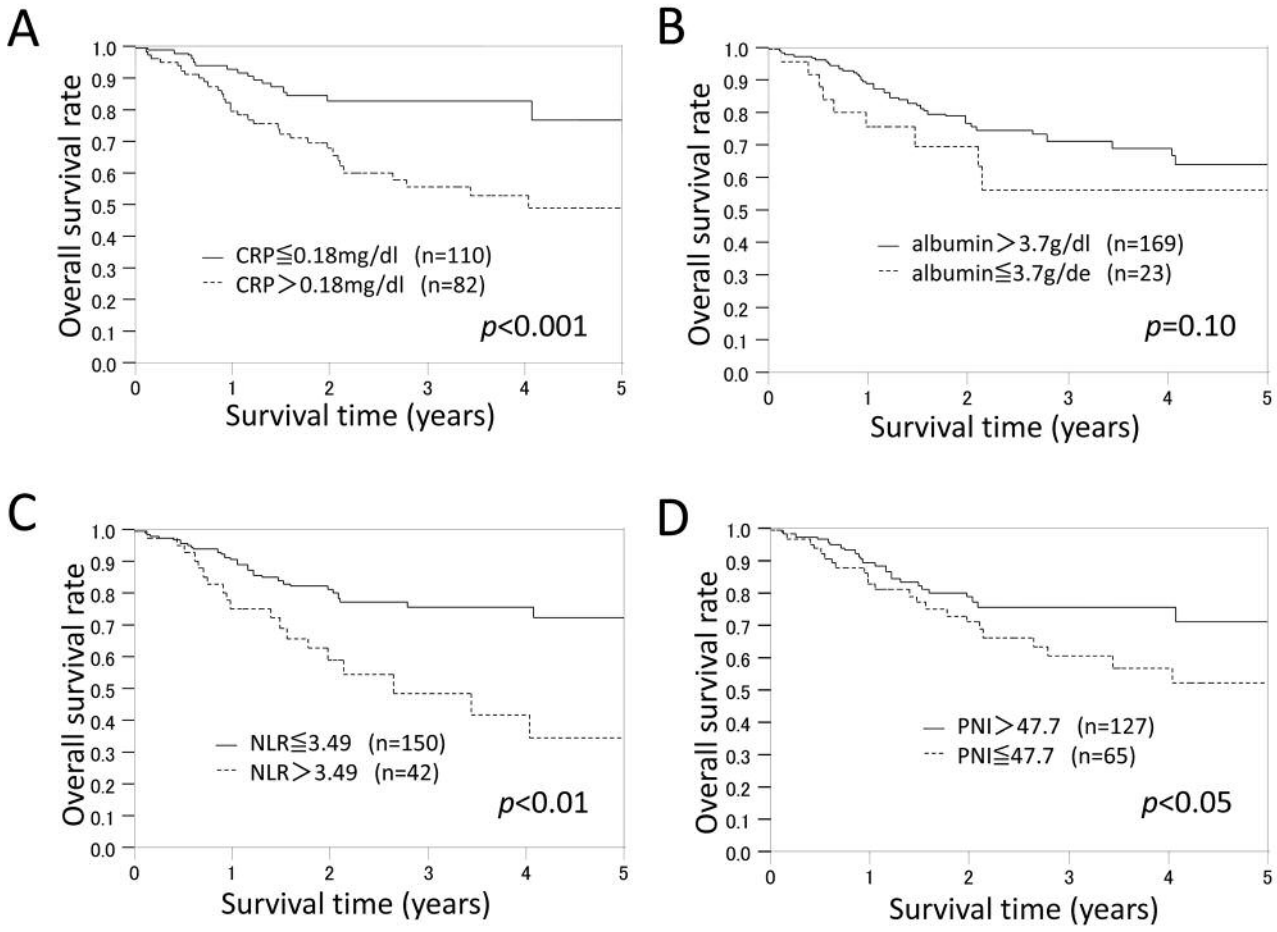

Figure 1. *Relationship between overall postoperative survival and variables. A: Patients in the high C-reactive protein (CRP) group (>0.18 mg/dl) had a significantly poorer prognosis than those in the low CRP group (≤0.18 mg/dl). B: Patients in the high albumin group (>3.7 g/dl) had a significantly more favorable prognosis than those in the low albumin group (≤3.7 g/dl). C: Patients in the high neutrophil-to-lymphocyte ratio (NLR) group (>3.49) had a significantly poorer prognosis than those in the low NLR group (≤3.49). D: Patients in the high nutritional index (PNI) group (>47.7) had a significantly more favorable prognosis than those in the low PNI group (≤47.7).*

in various organs (5). The results of their meta-analysis are highly suggestive for the role of PNI in cancer treatment, but only one study addressed esophageal cancer; thus, their results are not generally applicable to esophageal cancer treatment.

The preoperative NLR reflects the patient's inflammatory status, clinical stage, and survival rate for some malignancies (22-25). In their meta-analysis of esophageal cancer, Yodying *et al*. reported that the high NLR was associated with tumor progression and was predictive of poorer survival (8). In our study, the NLR was a prognostic factor in the univariate analysis but not in the multivariate analysis. CRP was also a prognostic factor in the univariate analysis. The patient's inflammatory status may play an important role in the survival of patients with esophageal cancer (26). In a recent meta-analysis, CRP was reported to be a prognostic factor in patients with esophageal cancer (10). The Glasgow prognostic score (GPS) has been also reported as a prognostic factor in patients who have undergone treatment for esophageal cancer (27, 28). In the current study, we did not evaluate the GPS because this score includes both CRP and serum albumin.

Conclusion

In the present study, the preoperative nutritional status was found to affect the postoperative survival time in patients with esophageal cancer. In particular, BMI was an independent prognostic factor in the multivariate analysis. We were unable to determine whether BMI was a cause or an effect; however, a low preoperative BMI may indicate poor prognosis. We used the amount of food intake as the basic indicator for

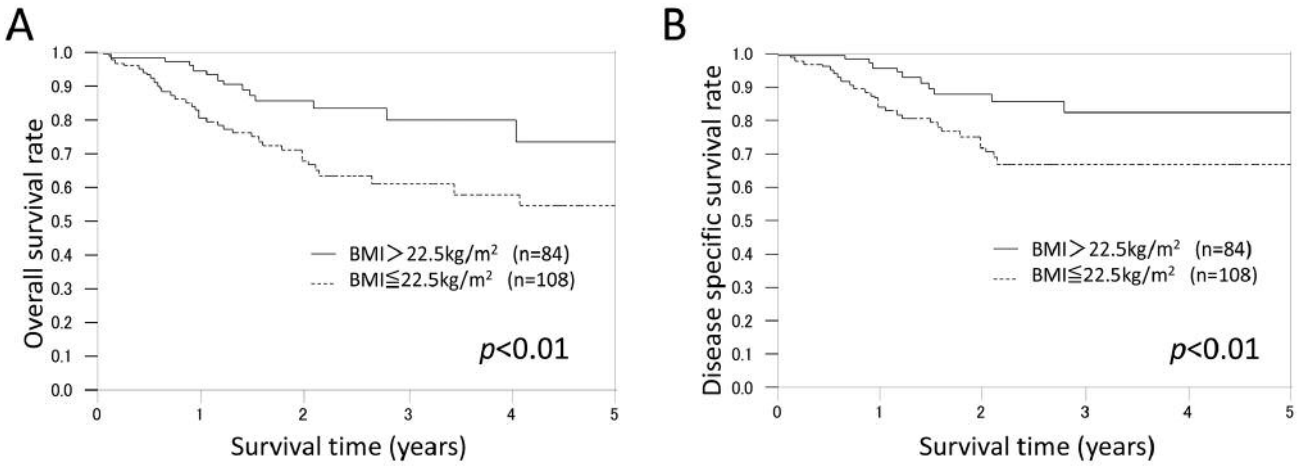

Figure 2. *Relationship between postoperative survival and body mass index (BMI). A: Relationship between overall postoperative survival and BMI. Patients in the high BMI group had a significantly more favorable prognosis than those in the low BMI group [5-year survival rates: high BMI group (>22.5 kg/m^2), 71.9%; low BMI group (≤22.5 kg/m^2), 53.6%; p<0.01]. B: Relationship between disease-specific postoperative survival and BMI. Patients in the high BMI group had a significantly more favorable prognosis than those in the low BMI group [5-year survival rates: high BMI group (>22.5 kg/m^2), 81.3%; low BMI group (≤22.5 kg/m^2), 66.2%; p<0.01].*

nutritional support. However, the BMI may be more important for the postoperative prognosis. Management of nutritional support is clearly of importance during the preoperative treatment of patients with esophageal cancer.

Funding

This work was supported in part by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) [grant numbers 26461938, 26461969, 15K10129, 15K20902].

References

1 Parkin DM, Bray FI and Devesa SS: Cancer burden in the year 2000. The global picture. Eur J Cancer *37(Suppl 8)*: S4-66, 2001.

2 Pennathur A, Gibson MK, Jobe BA and Luketich JD: Oesophageal carcinoma. Lancet *381*: 400-412, 2013.

3 Filip B, Scarpa M, Cavallin F, Cagol M, Alfieri R, Saadeh L, Ancona E and Castoro C: Postoperative outcome after oesophagectomy for cancer: Nutritional status is the missing ring in the current prognostic scores. Eur J Surg Oncol 41: 787-794, 2015.

4 Han L, Song Q, Jia Y, Chen X, Wang C, Chen P, Min R and Cheng Y: The clinical significance of systemic inflammation score in esophageal squamous cell carcinoma. Tumor Biol *37*: 3081-3090, 2016.

5 Sun K, Chen S, Xu J, Li G and He Y: The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin *140*: 1537-1549, 2014.

6 Zhang SS, Yang H, Luo KJ, Huang QY, Chen JY, Yang F, Cai XL, Xie X, Liu QW, Bella AE, Hu RG, Wen J, Hu Y and Fu JH: The impact of body mass index on complication and survival in resected oesophageal cancer: a clinical-based cohort and meta-analysis. Br J Cancer 109: 2894-2903, 2013.

7 Hanahan D and Weinberg RA: Hallmarks of cancer: the next generation. Cell *144*: 646-674, 2011.

8 Yodying H, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M and Uchida E: Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg Oncol *23*: 646-654, 2016.

9 McMillan DC, Canna K and McArdle CS: Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg *90*: 215-219, 2003.

10 Zheng TL, Cao K, Liang C, Zhang K, Guo HZ, Li DP and Zhao S: Prognostic value of C-reactive protein in esophageal cancer: a meta-analysis. Asia-Pac J Cancer Prev *15*: 8075-8081, 2014.

11 Duan H, Zhang X, Wang FX, Cai MY, Ma GW, Yang H, Fu JH, Tan ZH, Meng YQ, Fu XY, Ma QL and Lin P: Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma. World J Gastroenterol *21*: 5591-5597, 2015.

12 Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, Altorki NK and Abrams JA: Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol *18*: 3362-3369, 2011.

13 Sobin LH, Gospodarowicz MK, Wittekind C and International Union against Cancer. TNM classification of malignant tumours. 7th ed. Wiley-Blackwell, Chichester, West Sussex, UK; Hoboken, NJ, 2010.

14 World Health Organization CoO (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. World Health Organization, Geneva, Switzerland, 2000.
15 Onodera T, Goseki N and Kosaki G: Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai zasshi *85*: 1001-1005, 1984.
16 Miyazaki T, Kuwano H, Kato H, Yoshikawa M, Ojima H and Tsukada K: Predictive value of blood flow in the gastric tube in anastomotic insufficiency after thoracic esophagectomy. World J Surg *26*: 1319-1323, 2002.
17 Matsuda S, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Omori T and Kitagawa Y: Cumulative prognostic scores based on plasma fibrinogen and serum albumin levels in esophageal cancer patients treated with transthoracic esophagectomy: comparison with the Glasgow prognostic score. Ann Surg Oncol *22*: 302-310, 2015.
18 Buzby GP, Mullen JL, Matthews DC, Hobbs CL and Rosato EF: Prognostic nutritional index in gastrointestinal surgery. Am J Surg *139*: 160-167, 1980.
19 Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D and Sugimachi K: Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. Eur J Surg Oncol *28*: 396-400, 2002.
20 Nozoe T, Kohno M, Iguchi T, Mori E, Maeda T, Matsukuma A and Ezaki T: The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surg today *42*: 532-535, 2012.
21 Watanabe M, Iwatsuki M, Iwagami S, Ishimoto T, Baba Y and Baba H: Prognostic nutritional index predicts outcomes of gastrectomy in the elderly. World J Surg *36*: 1632-1639, 2012.
22 Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP and Prasad KR: Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg *32*: 1757-1762, 2008.
23 Kim JH, Han DS, Bang HY, Kim PS and Lee KY: Preoperative neutrophil-to-lymphocyte ratio is a prognostic factor for overall survival in patients with gastric cancer. Ann Surg Treat Res *89*: 81-86, 2015.
24 Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P and Lim E: Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg *137*: 425-428, 2009.
25 Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF and Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst *106*: dju124, 2014.
26 Nozoe T, Saeki H and Sugimachi K: Significance of preoperative elevation of serum C-reactive protein as an indicator of prognosis in esophageal carcinoma. Am J Surg *182*: 197-201, 2001.
27 Feng JF, Zhao Q and Chen QX: Prognostic significance of Glasgow prognostic score in patients undergoing esophagectomy for esophageal squamous cell carcinoma. Saudi J Gastroenterol *20*: 48-53, 2014.
28 Vashist YK, Loos J, Dedow J, Tachezy M, Uzunoglu G, Kutup A, Yekebas EF and Izbicki JR: Glasgow Prognostic Score is a predictor of perioperative and long-term outcome in patients with only surgically treated esophageal cancer. Ann Surg Oncol *18*: 1130-1138, 2011.

Received October 11, 2016
Revised October 31, 2016
Accepted November 1, 2016