

Prognostic value of an inflammation-based score in patients undergoing pre-operative chemotherapy followed by surgery for esophageal cancer

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Received April 21, 2011; Accepted June 7, 2011

DOI: 10.3892/etm.2011.308

Abstract. Recent studies have shown that the presence of systemic inflammation is associated with poor outcome in patients with malignancy. However, whether systemic inflammation affects the response to pre-operative therapy and survival of patients undergoing multimodal treatment for esophageal cancer is not clear. We studied 152 patients who underwent pre-operative chemotherapy followed by surgery for esophageal cancer. The correlation between various clinicopathological factors, including hematological markers of systemic inflammatory response, and survival or response to chemotherapy was examined. Among various hematological factors, leucocyte count, hemoglobin level, albumin level, neutrophil-lymphocyte ratio and CEA, but not serum concentration of C-reactive protein, were significantly associated with survival. Multivariate analysis revealed that the clinical response to chemotherapy, number of metastatic lymph nodes, operative complications and systemic inflammation score (SI score), comprising leucocyte count, albumin and hemoglobin levels, were independent prognostic factors, and identified the SI score as the most significant prognostic factor. There was no significant relationship between hematological markers of systemic inflammation, including the SI score, and the response to chemotherapy. In conclusion, in patients scheduled for chemotherapy followed by surgery for esophageal cancer, systemic inflammation, reflected by SI, predicts poor outcome, but not the response to chemotherapy.

Introduction

Esophagectomy is the standard treatment for esophageal cancer. However, the majority of patients who undergo curative

resection subsequently develop local or systemic recurrence, and the 5-year survival rate ranges from 15 to 39% (1,2). To improve prognosis, the combination of peri-operative chemotherapy and/or radiotherapy is used in conjunction with esophagectomy. Neoadjuvant chemoradiotherapy followed by surgery is one of the most promising strategies for advanced esophageal cancers, and several studies have reported survival advantages of this trimodality therapy compared with surgery alone (3-5). Another potential combination therapy is neoadjuvant chemotherapy followed by surgery, and several studies have reported encouraging results (6-8). Thus, multimodal treatment combining surgery with other treatments has achieved mainstream status as a curative therapy for advanced esophageal cancer.

Recently, there is increasing evidence that a systemic inflammatory response is of prognostic value in patients with various types of cancers. Elevated serum C-reactive protein concentration is associated with poor prognosis in colorectal, breast and ovarian cancers (9-11). Another commonly used biomarker for systemic inflammation is serum albumin concentration. Low serum albumin concentration, often in combination with elevated C-reactive protein, is reported to be a predictor of poor prognosis in various types of cancers including colorectal cancers (12-14). In esophageal cancers, previous studies have also shown that serum C-reactive protein as a biomarker of systemic inflammation is useful for predicting the prognosis of patients undergoing esophagectomy (15-18). However, whether such serum biomarkers correlate with the outcome of pre-operative therapy and survival of patients undergoing multimodal treatment is not clear at present.

In the present study, we determined whether the presence of systemic inflammation predicts the outcome of pre-operative chemotherapy and survival of patients undergoing pre-operative chemotherapy followed by surgery for advanced esophageal cancers. Moreover, we also established a scoring system for systemic inflammation that reflects prognosis of the same patients.

Materials and methods

Patient population. From April 2000 to September 2008, 385 patients with thoracic esophageal cancers underwent

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Key words: esophageal cancer, chemotherapy, inflammation, albumin, hemoglobin

surgery at the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University. Among these, 152 patients who received pre-operative chemotherapy followed by surgery were enrolled in the present study. All patients were newly diagnosed and had received no prior treatment. Basically, during the same period, patients with any T (cT1-4) and lymph node involvement, including regional lymph nodes (N1) and distant lymph nodes (M1 lym) without distant organ metastasis received pre-operative chemotherapy followed by surgery. All patients were younger than 80 years of age; had adequate cardiac, hepatic, renal and bone marrow reserve; and could tolerate both the planned chemotherapy and the following surgical procedures.

In this study, all patients were staged before and after surgery according to the criteria of the International Union Against Cancer (UICC). Pre-treatment clinical staging was based on endoscopy, computed tomography (CT) scans of the neck, chest and the upper abdomen as continuous 5-mm slices, and positron emission tomography (PET) scan. Lymph nodes were diagnosed as metastasis-positive on CT scan when they were >1.0 cm in maximum transverse diameter. Lymph nodes visible but <1.0 cm on the long axis on CT scan were regarded as metastasis-positive only when focal prominent 18-fluorodeoxy glucose (FDG) uptake, compared with normal mediastinal activity, was detected on the PET scan. The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine.

Hematological examination. Routine laboratory tests for leucocyte, neutrophil and lymphocyte counts, hemoglobin, albumin, C-reactive protein, carcinoembryonic antigen (CEA) and squamous cell carcinoma (SCC) antigen were carried out before the commencement of pre-operative chemotherapy. The serum concentration of C-reactive protein was measured using latex immunonephelometry method (normal range, 0-0.2 mg/dl). Serum levels of CEA and SCC antigen were measured using an enzyme immunoassay method. Serum levels <5 ng/ml for CEA and <2 ng/ml for SCC antigen were considered normal in this assay, respectively.

The systemic inflammatory score (SI score) was estimated as follows; a high leucocyte count ($>9,500$ μ l), low serum albumin level (<3.5 g/dl) and low hemoglobin level (<12.5 mg/dl) was each allocated a score of 1. SI score was calculated by adding up the scores of the leucocyte count, albumin and hemoglobin (range of SI score, 0-3).

Treatment protocol. Pre-operative chemotherapy administered at our hospital consisted of cisplatin, adriamycin and 5-fluorouracil (5-FU) (19). Cisplatin was administered at 70 mg/m², adriamycin at 35 mg/m² by rapid intravenous infusion on Day 1; and 5-FU at 700 mg/m² administered by continuous intravenous infusion on Day 1-7. Two courses of chemotherapy were used, separated by a 4-week interval. All patients underwent surgery 3 to 5 weeks after completion of pre-operative chemotherapy.

With regard to the type of surgery, 146 patients underwent transthoracic esophagectomy with two- or three-field lymphadenectomy while 6 patients underwent esophagectomy through trans-hiatal approach. Complete tumor resection (R0) was performed in 142 patients, while 10 patients had incomplete

tumor resection with microscopic (R1) or macroscopic residual tumors (R2). Peri-operative complications were observed in 57 (37.5%) of the 152 patients, including pneumonia/respiratory failure in 27, anastomotic leakage in 17, wound infection in 15, recurrent nerve palsy in 15, arrhythmia in 6, ischemia related to gastric tube in 3, chylothorax in 3, bleeding in 3, abdominal abscess in 2, cardiovascular failure in 3 and renal dysfunction in 2.

Evaluation of response to chemotherapy. In order to evaluate the clinical response to chemotherapy, 2 weeks after completion of chemotherapy, all patients were re-staged by endoscopy, CT scan, and PET scan. The clinical response was categorized according to the World Health Organization response criteria for measurable disease and the criteria of the Japanese Society for Esophageal Diseases (20). A complete response (CR) was defined as clinical complete regression of the disease. A CR of the primary tumors represented complete disappearance of the tumors on CT scan and/or PET scan and endoscopy, and excluded those confirmed to have further ulceration on endoscopy and cancer cells in endoscopically obtained biopsy samples. A partial response (PR) was defined as $>50\%$ reduction in primary tumor size and lymph node metastasis, as confirmed by CT scan. Progressive disease (PD) was defined as $>25\%$ increase in the primary tumor or the appearance of new lesions. Cases that did not meet the criteria of PR or PD were defined as stable disease (SD).

The degree of histopathological tumor regression in surgical specimens was classified into 5 categories. The extent of viable residual carcinoma at the primary site was assessed semi-quantitatively, based on the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumor bed that was evaluated histopathologically. The percentage of viable residual tumor cells within the entire cancerous tissue was assessed as follows: grade 3, no viable residual tumor cells; grade 2, $<1/3$ residual tumor cells; grade 1b, $1/3$ - $2/3$ residual tumor cells; grade 1a, $>2/3$ residual tumor cells; grade 0, no significant response to chemotherapy (19,20). The extent of residual carcinoma in regional lymph nodes was not assessed.

Follow-up study. Following hospital discharge, patients were examined every 2 months for the first 2 years, and every 3 months thereafter. Computed tomography of the neck, thorax and upper abdomen was performed every 4 months for the first 2 years and every 6 months thereafter. Upper gastrointestinal endoscopy was performed annually. Recurrence was confirmed by CT scan and, when necessary, PET scan. All data were collected, entered prospectively into a database and updated at regular intervals. The median follow-up period of all 152 patients was 60.2 months (range, 20.1-120.8).

Statistical analysis. Overall survival was calculated from the date of surgery to the occurrence of the event or to the last known date of follow-up. Actual survival was calculated by the Kaplan-Meier method and statistically evaluated by the log-rank test. The Cox proportional hazards regression model was used to analyze the simultaneous influence of prognostic factors. The relationships between SI score and various clinicopathological factors were examined by the Mann-Whitney U

Table I. Characteristics of the 152 patients who underwent pre-operative chemotherapy followed by surgery for esophageal cancers.

Variable	n
Age (years), mean \pm SD	62.5 \pm 8.4
Gender	
Male	132
Female	20
Tumor location	
Upper third	18
Middle third	63
Lower third	71
Tumor depth	
cT1	6
cT2	30
cT3	84
cT4	32
Lymph node involvement	
cN0	9
cN1	143
Tumor stage	
cStage II	30
cStage III	77
cStage IV	45

test. In all analyses, a $P < 0.05$ was accepted as statistically significant. These analyses were carried out using StatView J5.0 software package (Abacus Concepts, Inc., Berkeley, CA).

Results

Prognostic significance of systemic inflammatory response. Table I lists the characteristics of the patients who underwent pre-operative chemotherapy followed by surgery. The majority of patients were males and had squamous cell carcinoma with lymph node metastasis. Among various hematological factors including biomarkers for systemic inflammation such as C-reactive protein and albumin, we first identified predictors of prognosis of patients undergoing pre-operative chemotherapy. In this study, a C-reactive protein concentration >1.0 mg/dl and albumin level <3.5 mg/dl were considered to reflect the presence of systemic inflammation, based on previous studies (9,12-14). Upon univariate analysis, the leucocyte count, hemoglobin, albumin level and CEA were significantly associated with survival, while the serum concentration of C-reactive protein was not (Table II and Fig. 1). The neutrophil-lymphocyte ratio, which was reported previously to be a potential marker of inflammation (21,22), was also a significant factor influencing patient survival. In addition to these hematological factors, univariate analysis showed that clinical tumor depth, clinical response to chemotherapy, pathological tumor depth, number of metastatic lymph nodes and operative complications were significantly correlated with prognosis. While leucocyte

Table II. Results of univariate analysis of overall survival.

Variable	Patients	HR	95% CI	P-value
Pre-treatment factors				
Age (years) ($<70/\geq 70$)	118/34	1.01	0.60-1.71	0.9545
Gender (Female/male)	20/132	1.04	0.55-1.96	0.9047
Body mass index (kg/m ²) ($\geq 18.5/<18.5$)	111/41	0.87	0.53-1.43	0.5811
Tumor location (Ut-Mt/Lt)	81/71	1.20	0.79-1.83	0.3929
Tumor depth (cT1-2/cT3-4)	36/116	1.82	1.04-3.20	0.0352
Lymph node involvement (cN0/cN1)	9/143	1.41	0.52-3.86	0.5001
Histology (SCC/others)	140/12	0.89	0.38-2.06	0.7814
Hematological factors				
Leucocyte count (/ μ l) ($<9500/\geq 9500$)	128/24	1.87	1.07-3.25	0.0271
Neutrophil count (/ μ l) ($<6000/\geq 6000$)	111/41	1.32	0.82-2.12	0.2602
Lymphocyte count (/ μ l) ($\geq 1500/<1500$)	93/59	1.06	0.67-1.66	0.8164
Neutrophil-lymphocyte ratio ($<4.0/\geq 4.0$)	107/45	1.63	1.03-2.58	0.0387
Hemoglobin (mg/dl) ($\geq 12.5/<12.5$)	114/38	1.91	1.21-3.01	0.0056
Albumin (g/dl) ($\geq 3.5/<3.5$)	102/50	2.03	1.33-3.12	0.0011
C-reactive protein (mg/dl) ($<1.0/\geq 1.0$)	109/43	1.22	0.75-1.97	0.4207
SI score (0-1/2-3)	123/29	2.72	1.68-4.42	<0.0001
CEA (ng/ml) ($<5.0/\geq 5.0$)	125/27	1.87	1.10-3.17	0.0205
SCC antigen (ng/ml) ($<2.0/\geq 2.0$)	131/21	1.20	0.65-2.24	0.5544
Post-treatment factors				
Tumor depth (ypT1-2/ypT3-4)	56/96	2.24	1.37-3.68	0.0013
No of metastatic lymph nodes ($<3/\geq 3$)	91/61	3.13	2.02-4.85	<0.0001
Clinical response (CR-PR/SD-PD)	(83/69)	1.72	1.12-2.63	0.0130
Pathological response (major/minor response)	24/128	1.13	0.63-2.05	0.6850
Operative complication (absent/present)	95/57	1.82	1.19-2.79	0.0060

HR, hazard ratio; 95% CI, 95% confidence interval; Ut, upper third; Mt, middle third; Lt, lower third; SI score, systemic inflammation score; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; major response, grade 2-3; minor response, grade 1b-0.

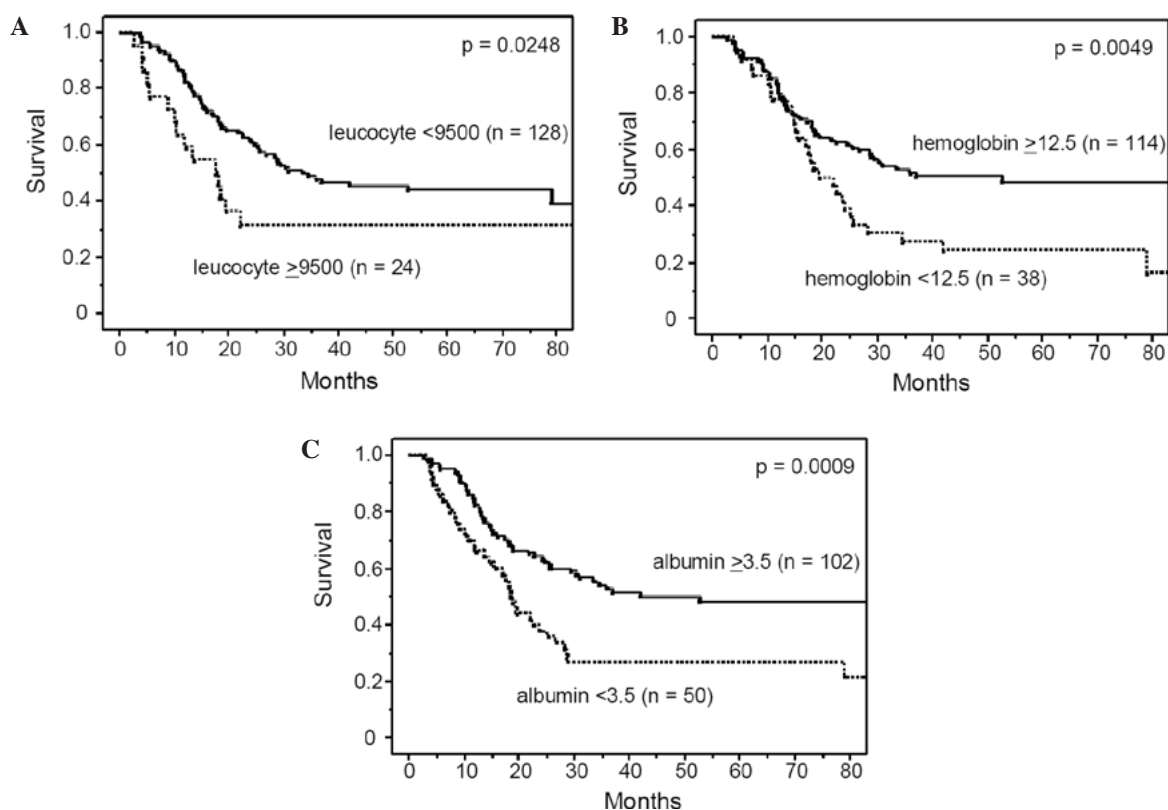


Figure 1. Overall survival rate of the 152 patients with esophageal cancers who received pre-operative chemotherapy followed by surgery, according to leucocyte count (A), hemoglobin level (B) and albumin level (C). The overall survival rates were significantly worse for patients with leucocytosis (≥9500), anemia (<12.5) and hypoalbuminemia (<3.5).

Table III. Results of the multivariate analysis of overall survival.

Variables		HR	95% CI	P-value
Initial tumor depth	cT1-2 vs. cT3-4	0.78	0.42-1.45	0.4463
Clinical response	CR-PR vs. SD-PD	1.78	1.08-2.94	0.0245
Neutrophil-lymphocyte ratio	(<4.0 vs. ≥4.0)	1.30	0.76-2.22	0.3362
SI score	(0-1 vs. 2-3)	3.17	1.74-5.78	0.0002
CEA (ng/ml)	(<5.0 vs. ≥5.0)	1.31	0.75-2.49	0.3362
Pathological tumor depth	(ypT1-2 vs. ypT3-4)	1.40	0.78-2.49	0.2565
No of metastatic lymph nodes	(<3 vs. ≥3)	3.12	1.92-5.08	<0.0001
Operative complication	(absent vs. present)	1.73	1.09-2.75	0.0204

HR, hazard ratio; 95% CI, 95% confidence interval; SI score, systemic inflammation score; CEA, carcinoembryonic antigen; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

count and albumin are well-known markers of systemic inflammation, cancer-related anemia in patients with cancer is also reported to be a marker of cancer-related chronic inflammation (23-25). Therefore, we established a systemic inflammation score (SI score) using a high leucocyte count, low serum albumin and low hemoglobin level, all of which were identified as significant prognostic factors in our univariate analysis. Multivariate analysis identified the clinical response, SI score, number of metastatic lymph nodes and operative complications as significant and independent prognostic factors, and identified SI score as the most significant prognostic factor, along with the number of metastatic lymph nodes (Table III and Fig. 2).

Relationship between systemic inflammation and clinico-pathological factors. Next, we examined the relationship between systemic inflammation (SI score) and various clinico-pathological factors, including response to pre-operative chemotherapy. The SI score was significantly correlated with clinical tumor depth, serum concentration of C-reactive protein and SCC antigen level (Table IV). Furthermore, intra-operative complications were more frequent in patients with a high SI score than those with a lower SI score. However, there was no significant relationship between SI score and response to chemotherapy, although the latter was an independent prognostic factor. There was also no significant relationship

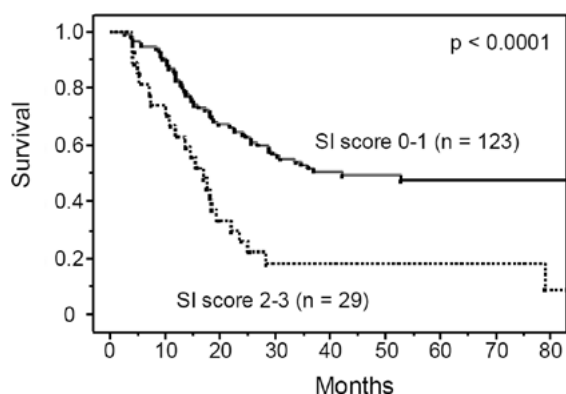


Figure 2. Overall survival rate of the 152 patients with esophageal cancers who received preoperative chemotherapy followed by surgery, according to the systemic inflammation score (SI score). The overall survival was significantly worse for patients with a high SI score (2-3), compared to patients with low SI score (0-1).

between response to chemotherapy and various hematological factors other than SI score, such as C-reactive protein and neutrophil/lymphocyte ratio.

Discussion

In the present study, we examined whether the presence of systemic inflammation affects prognosis and response to chemotherapy in patients undergoing pre-operative chemotherapy followed by surgery for advanced esophageal cancers. The results showed that the presence of systemic inflammation was associated with shortened survival of patients undergoing pre-operative chemotherapy but it had no significant influence on the response to chemotherapy. We also established a unique scoring system for systemic inflammation in patients undergoing multimodal treatment for esophageal cancers, which consisted of high leucocyte count, low serum albumin and low hemoglobin level. The SI score established in this study was identified as the most important prognostic factor on multi-variate analysis.

In previous studies, the most commonly used biomarker of systemic inflammation in malignant disease was serum C-reactive protein. C-reactive protein is produced in the liver and its production is regulated by pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 and tumor necrosis factor (TNF) α (26-28). Several previous studies demonstrated that a pre-operative high C-reactive protein level was inversely correlated with survival of patients with esophageal cancer (15-18). In these studies, the cutoff value of C-reactive protein ranged from 0.5 to 1.0 mg/dl. In this study, we attempted to use several cutoff values ranging from 0.5 to 1.0 mg/dl, but a high C-reactive value did not predict the survival of patients undergoing pre-operative chemotherapy/surgery for esophageal cancers, irrespective of the cutoff value.

Another commonly used biomarker of systemic inflammation in malignancy is the serum albumin concentration. Hypoalbuminemia, which is often used as an indicator of poor nutrition, is also known to correlate with systemic inflammation through high levels of pro-inflammatory cytokines (29-31). In esophageal cancer, Ikeda *et al* (17) reported that

Table IV. Relationship between clinicopathological factors and SI score.

Variables	n	SI score			P-value
		0	1	2-3	
No. of patients		83	40	29	
Age (years)					
<70	118	66	32	20	0.2480
\geq 70	34	17	8	9	
Gender					
Male	132	73	33	26	0.8511
Female	20	10	7	3	
cT					
cT1-2	36	27	6	3	0.0150
cT3-4	116	56	34	26	
cN					
cN0	9	5	2	2	0.4598
cN1	143	78	38	27	
C-reactive protein (mg/dl)					
<1.0	109	70	27	12	0.0002
\geq 1.0	43	13	13	17	
Neutrophil-lymphocyte ratio					
<4.0	107	68	26	13	0.0004
\geq 4.0	45	15	14	16	
CEA (ng/ml)					
<5	125	69	35	21	0.4271
\geq 5	27	14	5	8	
SCC antigen (ng/ml)					
<2	131	78	37	16	0.0002
\geq 2	21	5	3	13	
Clinical response					
CR-PR	83	45	18	20	0.6487
SD-PD	69	38	22	9	
Histopathology					
SCC	140	77	37	26	0.7984
Others	12	6	3	3	
pT					
pT1-2	56	33	12	11	0.7283
pT3-4	96	50	28	18	
No of metastatic lymph nodes					
<3	61	32	20	9	0.7695
\geq 3	91	51	20	20	
Pathological response					
Major response	24	10	4	10	0.0571
Minor response	128	73	36	19	
Operative complications					
Absent	95	58	23	14	0.0284
Present	57	25	17	15	

SI score, systemic inflammation score; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; major response, grade 2-3; minor response, grade 1b-0.

hypoalbuminemia was significantly correlated with poor survival of patients undergoing esophagectomy. Furthermore, recent studies also reported that hypoalbuminemia is predictive of the response to chemoradiotherapy and prognosis in patients treated by definitive chemoradiotherapy for esophageal cancers (32,33). Hypoalbuminemia is sometimes used in combination with elevated C-reactive protein to calculate the inflammation-based prognostic score, Glasgow Prognostic score. The Glasgow Prognostic score is reported to be useful in predicting survival of patients with colorectal cancers, non-small cell lung cancers, pancreatic cancers and breast cancers (12-14). In esophageal cancers, Crumley *et al* (34) demonstrated that the Glasgow Prognostic score predicts cancer-specific survival of patients with inoperable gastroesophageal cancers. Kobayashi *et al* (35) also reported that the Glasgow Prognostic score determined before treatment is an independent predictor of survival of patients undergoing neoadjuvant chemoradiotherapy followed by surgery although their study was limited to 48 cases only. In the present study, the serum albumin level, but not Glasgow Prognostic score, was a marker of prognosis of patients undergoing pre-operative chemotherapy followed by surgery.

Anemia is also a marker of chronic inflammation. In patients with inflammatory disorders, pro-inflammatory cytokines, such as TNF α , IL-1 and IFN- γ , do not only reduce the production of erythropoietin, which plays a crucial role in erythropoiesis, but also impair the response of erythroid progenitors to erythropoietin. In addition, the same pro-inflammatory cytokines can alter iron metabolism, leading to impaired erythropoiesis (24,25). A previous study demonstrated that a low hemoglobin level was negatively correlated with serum levels of IL-6, IL-1 β , C-reactive protein and TNF α in patients with ovarian cancer, suggesting that anemia in cancer is related to markers of inflammation (23). In the present study, a low hemoglobin level was associated with shortened survival of patients undergoing pre-operative chemotherapy for esophageal cancer, and we used a low hemoglobin level in addition to a low serum albumin concentration and high leucocyte count to estimate systemic inflammation. Thus, a low hemoglobin level is a potentially useful marker of systemic inflammation in patients undergoing multimodal treatment for advanced esophageal cancers.

The reason for our finding that systemic inflammation is not significantly associated with the response to chemotherapy but can predict survival of patients undergoing pre-operative chemotherapy followed by surgery is not clear. One possible explanation is that chronic inflammation may promote the spread of undetected cancer cells, micrometastasis, through polarization of M2 tumor-associated macrophages via cytokines, such as NF- κ B, and subsequent production of tumor growth factors or through the promotion of angiogenesis (36,37). Another plausible explanation is that chronic inflammation may be associated with compromised immune function such as impaired T-lymphocytic response via various pro-inflammatory cytokines and chemokines (38,39). In addition, this may lead to increased post-operative complications (40), which correlate with early cancer recurrence and poor prognosis (41,42). Indeed, our study showed that systemic inflammation was significantly correlated with a high incidence of post-operative complications. Further studies are needed to examine the relationship between systemic inflammation and response to chemotherapy.

In summary, we established a scoring index for systemic inflammation (SI score) that comprises high leucocyte count, low serum albumin and low hemoglobin level, to predict poor survival of patients undergoing pre-operative chemotherapy followed by surgery for esophageal cancer. Our study also found no significant relationship between SI score and response to pre-operative chemotherapy. However, the results showed that the SI score was the most important prognostic factor in patients undergoing multimodal treatment for esophageal cancer.

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