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Original Article

High and/or Non-Decreased Systemic Inflammatory Index During Treatment Indicates Poor Prognosis in Patients with Esophageal Cancer

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ABSTRACT

Introduction: The initial high systemic inflammatory index (SII), which is calculated as platelets × (neutrophils / lymphocytes), indicates a poor prognosis in patients with various malignant tumors, but its value after treatment in esophageal cancer is not well described.

Methods: The prognostic value of the perioperative SII was evaluated in 103 esophageal cancer patients treated by radical esophagectomy. Fifty-nine of the patients received neoadjuvant chemotherapy (NAC); 44 received surgery only. The prognostic value of the SII was evaluated at each stage of the treatment. The impact of clinicopathological factors on the SII and prognosis was also evaluated after stratifying patients by treatment with surgery and NAC or surgery only.

Results: Pre-treatment SII was not associated with prognosis, but pre-operative SII ($p = 0.11$), post-operative SII ($p = 0.07$), and post-NAC SII ($p < 0.05$) were associated with prognosis. A decrease in the SII during treatment was also associated with a good prognosis. A high SII before NAC was significantly associated with a decrease of SII during treatment ($p < 0.05$).

Conclusions: A high or non-decreased SII after treatment of esophageal cancer was a poor prognostic indicator. The prognosis of patients with high SSIs might be improved by NAC.

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KEYWORDS: neoadjuvant therapy, esophageal cancer, inflammatory index

Introduction

Surgery only, or neoadjuvant chemotherapy (NAC) plus surgery, are standard treatments of locally advanced esophageal cancer,[1] but the prognosis is poor even with advances in NAC and treatment of recurrent cancers. Pre-operative inflammation markers, such as the lymphocyte-to-monocyte, neutrophil-to-lymphocyte, and platelet-to-lymphocyte ratios,[2–7] and the systemic inflammatory index (SII), which is derived from neutrophil, platelet, and lymphocyte counts, have prognostic value in various cancers. It has been reported that the prognostic value of the SII, which composed of three parameters, is superior to that of the lymphocyte-to-monocyte, neutrophil-to-lymphocyte, or

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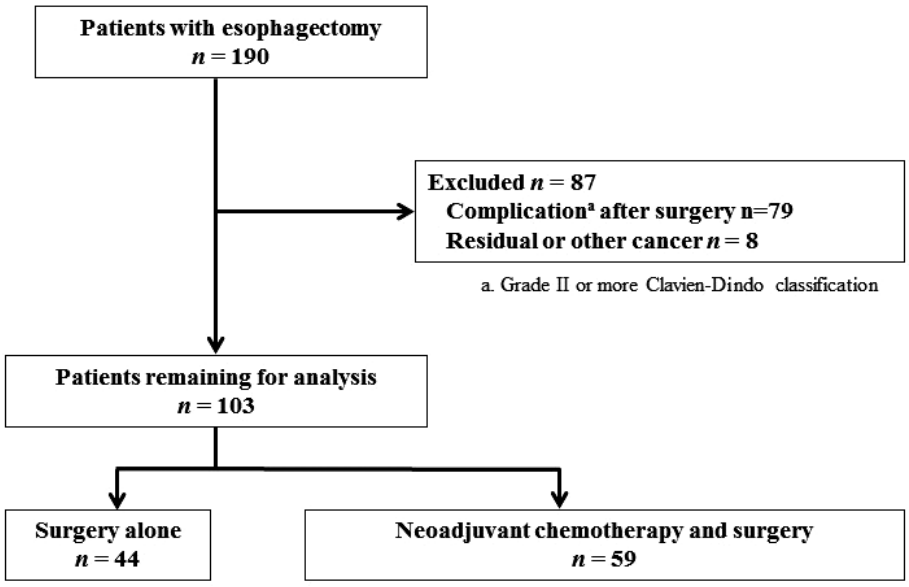

Fig. 1 A flowchart showing patient selection for the study. A total of 190 patients underwent esophagectomy for thoracic esophageal cancer. A total of 79 patients developed post-operative complications, classified as grade II or more of Clavien-Dindo classification. A total of eight patients revealed non-radical esophagectomy and/or combined with other cancers.

platelet-to-lymphocyte ratio which composed of two parameters.[8–11] Compared to molecular markers, the SII is convenient, easy to obtain, repeatable, and low-cost. Perioperative titers and changing biomarker values have been associated with poor prognosis or recurrence of cancer.[12, 13] Most studies have evaluated pre-treatment inflammatory indexes; few have evaluated post-treatment indexes.[14–17] The post-treatment SII and changes in the SII at each phase of treatment might be associated with prognosis. This study evaluated the clinicopathological and prognostic significance of peritreatment changes of the SII and the impact of NAC on the prognosis of patients with high SIIs.

Materials and Methods

Patients

The medical records of 103 patients with radical esophagectomy for esophageal cancer between November 2009 and March 2017 at the Omori Medical Center, Toho University School of Medicine were retrospectively reviewed (Fig. 1). Seventy-eight (75.7%) were men, 25 (24.3%) were women, and the median age was 66 (range 34-82). Fifty-nine had been treated with radical esophagectomy after NAC; 44 patients had been treated by surgery only. According to the treatment guideline, we usually apply NAC for stage II/III patients. We also applied NAC or NACRT for cervical esophageal (n=3) in order to preserve vocal cord. Patients with follow-up for three months after surgery, no other cancers, and no Clavien-Dindo grade II or higher post-operative complications were eligible. Twenty-eight patients satisfied the Union for International Cancer Control (UICC) criteria for clinical stage I and 75 for clinical stage II or III disease. Patients were followed-up until December 31, 2018, or their deaths. The median follow-up was 37 (range, 4-106) months. The overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. The study protocol was approved by the institutional review board of the Toho University (IRB #26-256).

SII calculation

Blood samples were collected before and after surgery, and just before chemotherapy in patients receiving NAC, for neutrophil, lymphocyte, and platelet counts. The blood samples before surgery in the NAC group were obtained within one week before surgery, and the blood samples after surgery were obtained in one to three months after surgery.

The SII was calculated as platelets × (neutrophils / lymphocytes). The median SIIs were 549 before treatment, 459 before surgery, and 510 after surgery. At each assess-

ment, patients with an SII below the cut-off value were included in a low SII group; those with an index above the cut-off value were included in a high SII group.

Patient characteristics

The patient characteristics included in the analysis were sex, age, UICC clinical stage, blood count, tumor markers, and C-reactive protein (CRP). The blood count included peripheral total white blood cells (WBCs), neutrophils, lymphocytes, and platelets. The tumor markers included serum p53 antibodies (s-p53-Abs) and squamous cell carcinoma antigen (SCC Ag). The CRP cut-off was 0.2 mg/dL and median values were used as WBC, neutrophil, lymphocyte, and platelet counts.

Treatment

Clinical stage II or III patients received NAC consisting of cisplatin 80 mg/m^2 on day one by intravenous drip infusion for 2 h and 5-fluorouracil 800 mg/m^2 by continuous infusion on days 1 through 5.[1)] NAC was given twice every three weeks. Patients with creatinine $>$ 1.2 mg/dL, blood urea nitrogen $>$ 25 mg/dL, creatinine clearance of $<$ 60 mL/min, total bilirubin $>$ 1.2 mg/dL, glutamic oxaloacetic transaminase $>$ 79 IU/L, glutamic pyruvate transaminase $>$ 62 IU/L, or hemoglobin $<$ 10 g/dL, PaO_2 $<$ 70 torr were not given NAC. Surgery was scheduled within 3-6 weeks after NAC. All patients underwent curative surgery with D2 lymphadenectomy.

Statistical analysis

The SII was expressed as means ± standard deviation, and the differences were evaluated for significance by Student's *t*-test. The OS was estimated by the Kaplan-Meier product limit method and differences between groups were evaluated with the Log-rank test. The prognostic significance of clinicopathological factors was evaluated by Log-rank test and Cox proportional hazard regression. The significance of clinicopathological factors to increase SII was evaluated by Fisher's exact probability test and Logistic regression analysis. Statistical analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander designed to add statistical functions frequently used in biostatistics. We determined $p<0.05$ as statistical significance level.

Results

Pre-treatment SII

Pre-treatment SII was significantly associated with sex, UICC clinical stage, pre-treatment CRP, and peripheral WBC, neutrophil, lymphocyte, and platelet counts, but not with age, pre-treatment s-p53-Abs, and SCC Ag (Table 1).

Overall survival of high SII

Pre-treatment SII was not associated with OS (p = 0.46, Fig. 2a). Although the differences were not significant, high pre-operative SII (p = 0.11) and high post-operative SII (p = 0.07) showed worse survival than low SII patients (Fig. 2). The median OS of pre-treatment high SII patients was 45 months (Fig. 2a). The median OS of pre-operative high SII patients was 48 months (Fig. 2b). The median OS of post-operative high SII patients was 45 months (Fig. 2c).

Risk factors predictive of OS

Univariate analysis found that the clinical UICC stage was a significant prognostic factor (Table 2). Multivariate analysis found that clinical UICC stage was the only risk factor independently associated with OS ($p < 0.01$).

Prognostic value of high SII in NAC patients

The OSs of patients with a high SII and those with a low SII at each stage of treatment in the NAC group are shown in Fig. 3. Pre-treatment SII was not associated with OS (p = 0.67, Fig. 3a). High post-NAC SII showed significantly worse survival than low SII patients ($p < 0.05$, Fig. 3b). Although the difference was not significant, high post-operative SII showed worse survival than low SII patients (p = 0.13, Fig. 3c).

Prognostic value of change in SII in NAC patients

The prognostic impact of a change in SII from pre-NAC to post-NAC, post-NAC to post-operation, and pre-NAC to post-operation evaluated for OS are shown in Fig. 4. Patients with a decrease in SII following NAC had a better prognosis than those without a decrease in the SII, but the difference was not statistically significant (Fig. 4a, p = 0.06). Patients with a decrease in SII between pre-NAC to post-operation had a significantly better prognosis (Fig. 4c, $p < 0.05$). A pre- to post-operation change in SII did not influence prognosis (Fig. 4b, p = 0.57). Fig. 5a-d shows the OS of patients with post-NAC SII/pre-NAC SII $\leq$ 1 (groups A and B), post-NAC SII/Pre-NAC SII $>$ 1 (groups C and D), post-operative SII/pre-NAC SII $\leq$ 1 (groups A and C) and post-operative SII/pre-NAC SII $>$ 1 (groups B and D). The nine patients in group D had the worst prognosis. The prognoses in the three other groups were similar and

Table 1 Comparisons of pretreatment systemic inflammatory indices according to clinicopathological factors and various biomarkers

Variables		Number of patients (n = 103)	SII[a] mean ± SD[b]	*p value*[c]	NAC[d] + Surgery (n = 59)	Surgery alone (n = 44)
Gender	Male	78	633 ± 356	0.03	47	31
	Female	25	894 ± 860		12	13
Age	< 65	48	715 ± 520	0.74	32	16
	≥ 65	55	680 ± 546		27	28
UICC cStage	I	28	495 ± 226	0.02	3	25
	II / III	75	770 ± 592		56	19
pre-treatment WBC counts (/ml^3)	≤ 8500	95	623 ± 368	< 0.01	53	42
	> 8500	8	1546 ± 1190		6	2
pre-treatment Neutrophil percentages	< median (60%)	51	401 ± 182	< 0.01	29	22
	≥ median (60%)	52	983 ± 602		30	22
pre-treatment Lymphocytes percentages	< median (29.1%)	53	983 ± 599	< 0.01	29	24
	≥ median (29.1%)	50	391 ± 156		30	20
pre-treatment Platelet counts (/ml^3)	< median (217000)	51	473 ± 241	< 0.01	22	29
	≥ median (217000)	52	913 ± 642		37	15
pre-treatment CRP (mg/dl)	≤ 0.2	64	561 ± 344	< 0.01	33	31
	> 0.2	39	916 ± 695		26	13
pre-treatment s-p53-Abs (U/ml)	≤ 1.3	78	702 ± 550	0.76	44	34
	> 1.3	22	663 ± 474		12	10
pre-treatment SCC Ag (ng/ml)	≤ 1.5	69	666 ± 521	0.44	40	29
	> 1.5	34	754 ± 558		19	15

a. SII, systemic inflammatory index
b. SD, standard deviation
c. Student's t-test
d. NAC, neoadjuvant chemotherapy

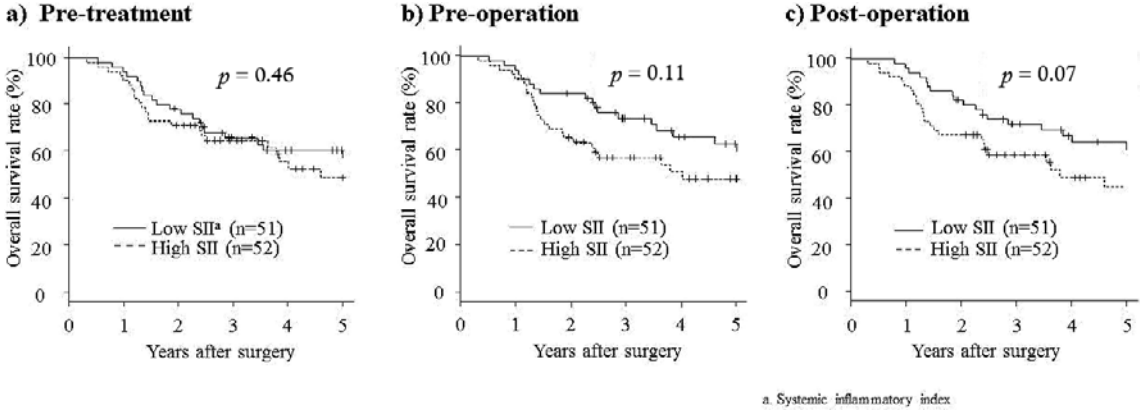

Fig. 2 Comparisons of overall survivals between high systemic inflammatory index group and low systemic inflammatory index group according to divided into two groups by median value of each phase systemic inflammatory index. a) cut-off value = 549, b) cut-off value = 459, c) cut-off value = 510.

were better than that in group D.

Peritreatment SII and biomarkers in NAC patients

The clinicopathological characteristics and SII values in the patients who received NAC are shown in Table 3. Pre-NAC SII was the only predictive factor for a decrease of the SII ($p < 0.05$). A high pre-NAC SII was significantly associated with a decrease in SII following treatment.

Discussion

The SII values and changes in SII during treatment

Table 2 Univariate and multivariate analysis of prognostic variables about a preoperative systemic inflammatory index with clinicopathological factors and various biomarkers

Variables			Univariate analysis	Multivariate analysis		
			p value[a]	H.R.[b]	95%CI[c]	*p value*[d]
Gender	Male	48	0.32	1.35	0.61	0.45
	Female	55				
Age	<65	25	0.90	1.04	0.57-1.91	0.9
	≥65	78				
UICC cStage	I	28	<0.05	6.67	2.01-22.10	<0.01
	II&III	75				
pre-treatment CRP (mg/dl)	≤0.2	64	0.07	0.99	0.52-1.91	0.98
	>0.2	39				
pre-treatment s-p53-Abs (U/ml)	≤1.3	78	0.80			
	>1.3	22				
pre-treatment SCC Ag (ng/ml)	≤1.5	82	0.17			
	>1.5	21				
Pre-operative SII	<median (459)	51	0.11	1.50	0.79-2.82	0.21
	≥median (459)	52				

a. Log-rank test
b. H.R. adjusted hazards ratio
c. 95%CI. Adjusted 95% confidence interval
d. Cox proportional hazard regression analysis

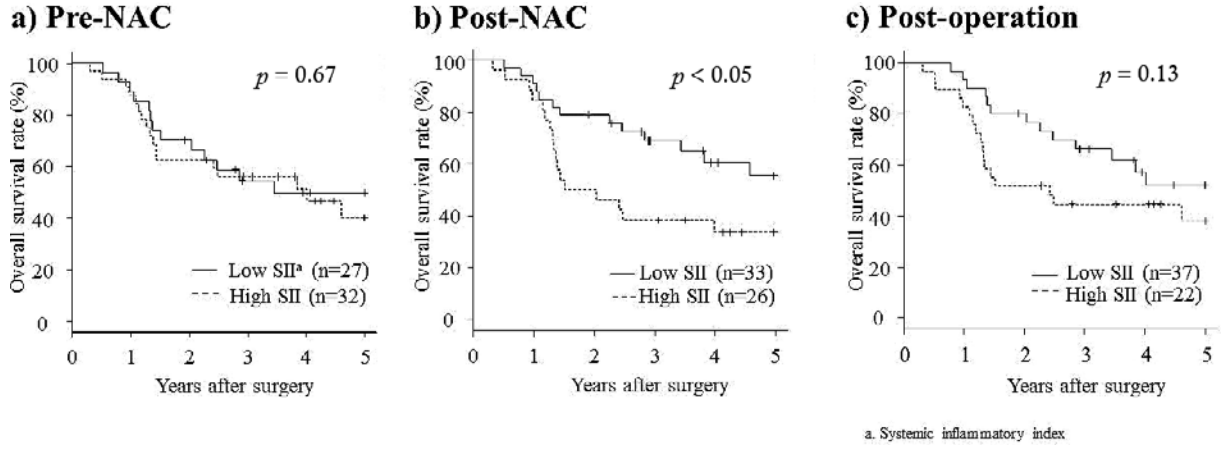

Fig. 3 Overall survivals in 59 patients treated with neoadjuvant chemotherapy and surgery. Comparisons between high systemic inflammatory index group and low systemic inflammatory index group at each phase of treatment. a) cut-off value = 549, b) cut-off value = 459, c) cut-off value = 510.

were significantly associated with prognosis in this series of patients with surgery for esophageal carcinoma. Pre-NAC SII was not a prognostic factor, but post-NAC SII and post-operative SII were prognostic factors. A decrease in SII was associated with improved OS, and NAC was more likely to reduce SII in patients with a high baseline index than in those with a low baseline index. The lack of prognostic impact of pre-treatment SII is not consistent with previous studies.[10, 11, 18–20]

In our series of patients, post-NAC SII was associated with survival. A decrease of SII after NAC might cancel the negative effects of a high SII on OS. The timing of data collection after surgery was very important, and the post-operative blood cell count varied by the time from the operation. We used blood cell counts at one to three months after operation when the data was not modified by surgical site infection.

Cut-off values of SII were also important. The definitive

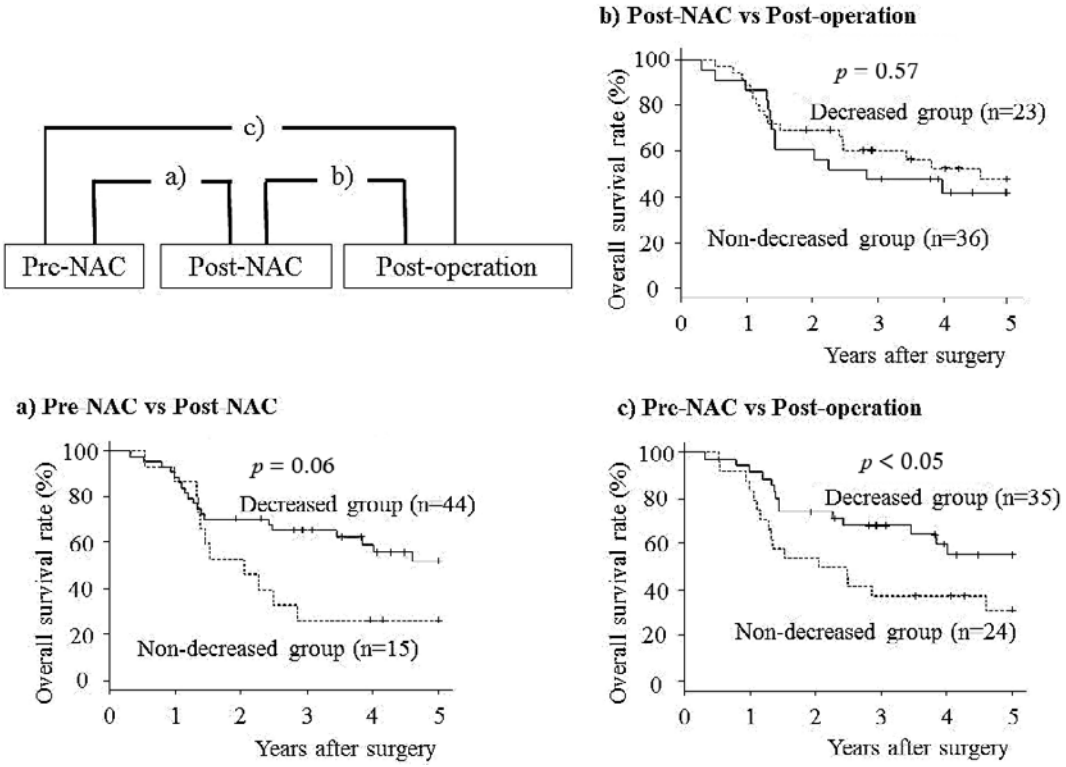

Fig. 4 Overall survivals in 59 patients treated with neoadjuvant chemotherapy and surgery. Comparisons between systemic inflammatory index decreased group and systemic inflammatory index non-decreased group at each phase of treatment. a) pre-neoadjuvant chemotherapy vs post-neoadjuvant chemotherapy, b) post-neoadjuvant chemotherapy vs post-operation, c) pre-neoadjuvant chemotherapy vs post-operation.

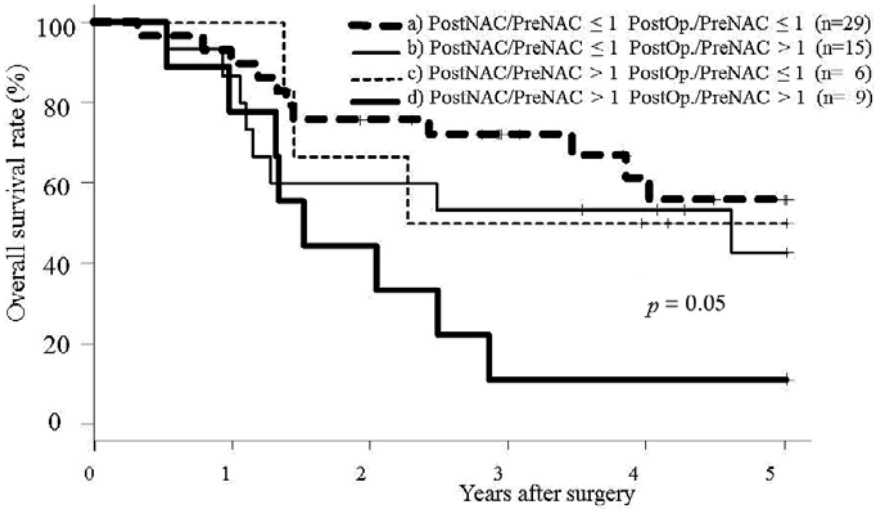

Fig. 5 Overall survivals in 59 patients treated with neoadjuvant chemotherapy and surgery. Comparisons between four groups according to changing patterns of the systemic inflammatory index at each treatment phase.

cut-off value of SII has not been determined. Previous reports determined the optimal cut-off values according to receiver operating characteristic curves to be 307 to 650.[10, 11, 18–20] In our series, we determined the cut-off values as median values at each phase. They were within the range of previously reported cut-off values (549 before

Table 3 Comparison between systemic inflammatory index increased group and systemic inflammatory index decreased group in patients with neoadjuvant chemotherapy followed by surgery

Variables	Number of patients (n = 59)	Univariate analysis			Multivariate analysis		
		Decreased group (n = 44)	Increased group (n = 15)	*p value*[a]	H.R.[b]	95%CI[c]	*p value*[d]
Gender	Male (47)	34	13	0.71	2	0.35-11.4	0.43
	Female (12)	10	2				
Age	＜65 (32)	24	8	1	0.72	0.19-2.71	0.63
	≧65 (27)	20	7				
UICC cStage	I (3)	3	0	0.56	3.32E＋07	0.00-Inf	0.99
	II/III (56)	41	15				
pre-NAC CRP (mg/dl)	≦0.2 (33)	25	8	1			
	＞0.2 (26)	19	7				
pre-NAC s-p53-Abs (U/ml)	≦1.3 (44)	32	12	0.71			
	＞1.3 (12)	10	2				
pre-NAC SCC Ag (ng/ml)	≦1.5 (40)	29	11	0.75			
	＞1.5 (19)	15	4				
pre-NAC SII	＜median 549 (27)	17	10	0.08	0.2	0.07-0.92	＜0.05
	≧median 549 (32)	27	5				

a. Fisher's exact probability test
b. H.R. adjusted hazard ratio
c. 95%CI adjusted 95% confidence interval
d. Logistic regression analysis

treatment, 459 before surgery, and 510 after surgery).

As CRP was associated with SII, these two parameters were evaluated separately in the multivariate analysis. When CRP was excluded from the multivariate analysis, SII was not an independent prognostic factor ($p = 0.19$). CRP itself was not an independent prognostic factor ($p = 0.82$). Although various serum tumor markers were useful in patients who were seropositive before treatment, SII can be calculated in all patients and SII monitoring during the treatment is more convenient than staging. A decrease of the SII between pre-NAC to post-NAC and pre-NAC to post-operation had a good prognosis, and more likely with NAC in patients with high than with low initial SII. It seems that patients with a high SII would benefit from NAC, and pre-treatment SII might be a useful indicator for selecting a good candidate for NAC. Nine patients had no reduction of SII during NAC and surgery. Eight of these nine patients died within five years. Such patients should be treated with post-operative adjuvant chemotherapy using regimens other than NAC. Although the changes of SII during NAC seemed to have prognostic impact, it should be considered that several adverse events are associated with bone-marrow suppression because of NAC and the effects of a granulocyte-colony stimulating factor. In our study, nine patients were received granulocyte-colony stimulating factor after NAC.

One of the study limitations is that we do not know whether the cancer increased the SII or the high SII was a surrogate marker of cancer cell growth. These study results might have been affected by perioperative complications.[21] Although 79 patients with Clavien-Dindo grade II or higher post-operative complications were excluded, it was difficult to completely exclude the influence of minor post-operative complication on SII. Further assessments should evaluate the impact of post-operative complications on changes of SII. The other limitation is that the number of patients analyzed in this study was too small to make definite conclusion. Further, large-scale studies should be performed to confirm our speculations.

In conclusion, the SII after treatment and peri-treatment changes of SII were prognostic indicators in patients with esophageal carcinoma. NAC reduced the SII, particularly in patients with high initial SIIs, which resulted in improved OS. Esophageal cancer patients with a high SII might be good candidates for NAC.

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Ethics Statement: All procedures were performed following the ethical guidelines of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients before study inclusion. This retrospective study was approved by the Institutional Review Board of the Toho University (Tokyo, Japan; Omori Hospital Ethics committee #26-256).

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