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Prognostic Value of the Perioperative Systemic Inflammation Score for Patients With Curatively Resected Gastric Cancer

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Abstract. *Background/Aim: The systemic inflammation score (SIS) is a promising tool for the evaluation of prognosis. The present study aimed to evaluate the clinical impact of the preoperative SIS status in gastric cancer (GC) patients who underwent curative resection. Patients and Methods: This study retrospectively analyzed 258 patients with primary gastric cancer who received curative treatment at Yokohama City University. The SIS was evaluated before surgery as determined by the lymphocyte-to-monocyte ratio (cut-off value=4.44) and serum albumin level (cut-off value=4.0 g/dl). Results: A high SIS was identified as an independent predictor of overall survival [hazard ratio (HR)=1.784, p<0.05] and multivariate analysis showed marginal significance for recurrence-free survival (HR=1.710, p<0.05). Conclusion: The preoperative SIS score was correlated with both the OS and RFS of GC patients, as well as the clinical course of adjuvant chemotherapy. Thus, the SIS score is a promising prognostic factor for GC.*

Gastric cancer was the fifth-most common cancer and the fourth most frequent cause of cancer-related mortality worldwide in 2020 (1). The standard treatment for locally advanced gastric cancer is gastrectomy and postoperative adjuvant chemotherapy.

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The 5-year survival rate is reported to be 96.7% for early-stage gastric cancer, and 51.9% for advanced gastric cancer (2, 3). The postoperative recurrence rate is 50%, and the 5-year survival rate after recurrence is <5%. Advanced gastric cancer still has an unfavorable prognosis. To improve the long-term prognosis of advanced gastric cancer, the risk of recurrence must be predicted, and more aggressive treatment must be given to those at high risk of recurrence.

Since Virchow first proposed the relationship between inflammation and cancer in 1863 (4), it has become clear that systemic inflammation plays an important role in the etiology and progression of cancer (5). Previous studies have shown that the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and preoperative serum pre-albumin, could be potentially used as predictors of the prognosis of cancer (5-7). However, these indicators only assess either the inflammatory or nutritional status.

Recently, the systemic inflammation score (SIS) has been reported to have an effect on the postoperative prognosis of colorectal and esophageal cancer (8, 9). SIS includes systemic inflammation and the nutritional status. Thus, it is a superior marker than any other single inflammatory or nutritional indicator. However, there are limited studies evaluating the clinical impact of the SIS in gastric cancer. This study therefore aimed to clarify whether preoperative SIS affects the short-term and long-term oncological outcomes in gastric cancer patients.

Patients and Methods

Patients. Patients were retrospectively selected from the medical records of consecutive patients diagnosed with primary gastric cancer who underwent gastrectomy at Yokohama City University from 2000 to 2015. The inclusion criteria were as follows: 1) histologically proven adenocarcinoma, according to the 15th edition of the Japanese Classification of Gastric Carcinoma (JCGC) published by the Japanese Gastric Cancer Association (JCGC) (10), 2) complete (R0) resection of gastric cancer with lymphadenectomy (D1 or more) as a primary treatment, 3) stage I-III disease diagnosed pathologically

Table I. *Comparison of survival rates stratified by patient characteristics*.

Characteristics	No. of patients (%)	1-year OS rate (%)	3-year OS rate (%)	5-year OS rate (%)	*p*-Value
Age (years)					<0.001
<75	179 (69.3)	96.9	82.8	78.6	
≥75	79 (30.7)	96.0	65.9	52.7	
Sex					0.416
Male	183 (70.9)	97.6	75.7	69.8	
Female	75 (29.1)	94.3	80.8	72.2	
Site of tumor					0.009
Upper	63 (24.4)	93.4	62.6	55.2	
Middle	113 (43.8)	96.0	81.3	78.1	
Lower	82 (31.8)	97.3	84.5	73.2	
T status					<0.001
T1	138 (53.5)	99.1	94.9	91.7	
T2 to T3	120 (46.5)	93.0	59.4	50.0	
Lymph node metastasis					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Systemic Inflammation Score					<0.001
0	171 (66.3)	98.1	84.6	78.2	
1	37 (14.3)	93.8	64.5	64.5	
2	50 (19.4)	93.6	62.8	50.6	
Lymphatic invasion					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Vascular invasion					<0.001
Negative	154 (59.7)	98.5	90.5	85.1	
Positive	104 (40.3)	92.9	60.8	51.6	
Postoperative surgical complications					0.003
No	160 (62.0)	98.5	90.5	85.1	
Yes	98 (38.0)	92.9	60.8	51.6	
Histological type					0.106
Intestinal	137 (53.1)	97.5	83.3	75.0	
Diffuse	121 (46.9)	94.8	72.1	66.3	

OS: Overall survival.

based on the 15th edition of the JCGC, and 4) a laboratory blood analysis, including serum albumin (Alb) and the white blood cell (WBC) count, in order to determine the SIS within one week before surgery. Patients who were diagnosed with remnant gastric cancer, who had received preoperative chemotherapy, and who had synchronous or multiple cancers, or whose medical records were incomplete or inaccurate were excluded.

Surgical procedure and adjuvant treatment. All patients underwent distal or total gastrectomy with lymph node dissection. D1+nodal dissection was performed for clinical stage IA disease, while D2 dissection was performed for clinical stage ≥IB. Patients with a pathological diagnosis of II or III received one year of postoperative adjuvant chemotherapy. As a rule, patients with pathological stage II disease were treated with S-1 monotherapy, and patients with pathological stage III disease were treated with S-1 in combination with docetaxel or capecitabine plus oxaliplatin.

SIS definition. SIS was calculated by the perioperative Alb level and LMR. According to previous studies, a score of 0 was defined as Alb ≥4.0 g/dl and LMR ≥4.44; a score of 1 was defined as either Alb <4.0 g/dl or LMR <4.44; and a score of 2 was defined as Alb <4.0 g/dl and LMR <4.44. The SIS was evaluated within seven days prior to surgery (11).

Evaluations and statistical analyses. The significance of differences between the SIS and clinicopathological parameters was determined by the χ^2 test. Overall survival (OS) and recurrence-free survival (RFS) curves were calculated by the Kaplan–Meier method. Univariate and multivariate survival analyses were analyzed using a Cox proportional hazards model. *p*-Values <0.05 were considered to be statistically significant.

Results

Patients. A total of 258 patients were assessed in this study. Based on the 1-,3- and 5-year OS rates, a cutoff value of 2 for SIS was used for the preset study (Table I). Of the 258 total patients, 171 (66.3%) were classified in the Low-SIS group, and 87 (33.7%) in the High-SIS group.

On comparing background characteristics between the Low- and High-SIS groups, the findings were quite similar. The

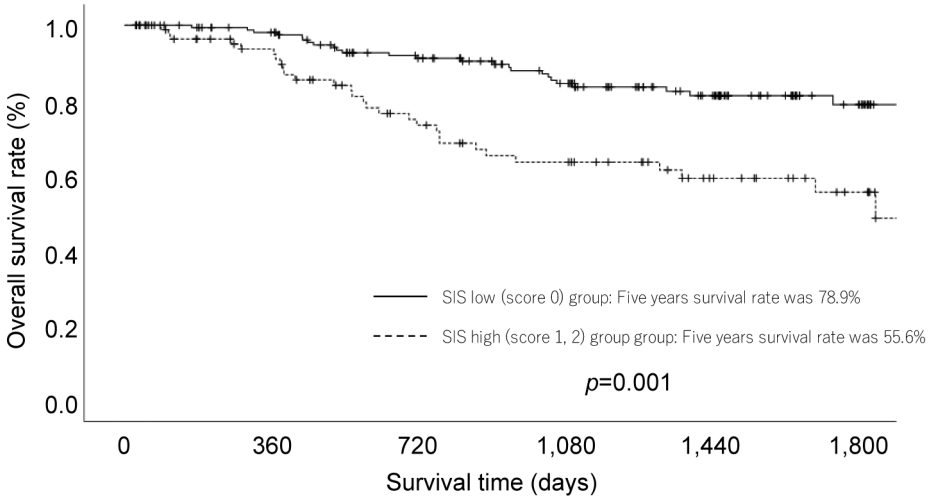

Figure 1. *Overall survival in the High-systemic inflammation score (SIS) and Low-SIS groups.*

proportions of males (69.6% *vs*. 73.6%, p=0.506), individuals with an alcohol habit (68.4% *vs*. 66.7%, p=0.775), individuals with a smoking habit (65.5% *vs*. 60.9%, p=0.469), incidence of hypertension (38.6% *vs*. 40.2%, p=0.799), and morbidity of chronic obstructive pulmonary disease (33.3% *vs*. 44.8%, p=0.071) were equivalence in the Low- and High-SIS groups, while the median age (66.4 years *vs*. 72.9 years, p<0.001), morbidity of diabetes mellitus (15.2% *vs*. 25.3%, p=0.049) and median body mass index were considerably higher in the High-SIS group (22.9 *vs*. 21.9, p=0.014).

Survival of the Low- and High-SIS groups. The 3- and 5-year OS rates were 83.6% and 78.9%, respectively, in the Low-SIS group and 61.5% and 55.6% in the High-SIS group, which amounted to a statistically significant difference (Figure 1) (p=0.001). Each clinicopathological factor was classified as shown in Table II and evaluated for its prognostic value. The univariate analysis of OS showed pathologic T factor and SIS to be statistically significant prognostic factors. The SIS was set for the final multivariate analysis model [hazard ratio (HR)=1.784, 95% confidence interval (CI)=1.039-3.063, p<0.05]. The respective 3- and 5-year RFS rates were 45.3% and 77.4% in the Low-SIS group and 21.4% and 48.6% in the High-SIS group, showing a statistically significant difference (Figure 2) (p=0.001). Each clinicopathologic factor was categorized and its prognostic value analyzed as shown in Table III. Univariate analysis of RFS showed that pathologic factors and SIS were significant prognostic factors. The SIS was therefore also selected for the final multivariate analysis model (HR=1.710, 95%CI=1.027-2.847, p<0.05). When comparing the site of recurrence, there were significant differences in the rates of hematological recurrence and local recurrence between the High- and Low-SIS groups (Table IV).

Clinical course of adjuvant treatment and postoperative complications between the Low- and High-SIS groups. When comparing the patients who required adjuvant treatment after surgery between the Low- and High-SIS groups, 32.2% (55/171) of the patients were eligible for adjuvant treatment in the Low-SIS group, while 59.8% (52/87) were eligible in the High-SIS group. The difference was statistically significant (p<0.001). On the other hand, when comparing the rate of adjuvant treatment after surgery between the Low- and High-SIS groups, 74.1% (14/40) of patients in the Low-SIS group and 49.0% (25/51) of the patients in the High-SIS group received adjuvant treatment. The difference was statistically significant (p=0.08). The postoperative surgical complication rate was 37.4% (64/171) in the Low-SIS group and 39% (34/87) in the High-SIS group (p=0.796). Regarding the details of postoperative complications, the incidence rates in the Low-SIS *vs*. High-SIS groups were as follows: postoperative pneumonia, 7% *vs*. 3.4%; (p=0.247); anastomotic leakage, 7% *vs*. 11.5% (p=0.224); abdominal abscess, 2.9% *vs*. 3.4% (p=0.818); and anastomotic stenosis, 1.2% *vs*. 0% (p=0.672). There were no significant differences.

Discussion

The objective of this study was to identify the clinical value of the preoperative SIS as a prognostic factor for curative resection of gastric cancer. The major findings were that the preoperative SIS was a significant prognostic factor for gastric cancer patients undergoing curative resection. In

Table II. *Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors for overall survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.002			
<75	179	1.000					
≥75	79	2.288	1.351-3.875				
Sex				0.467			
Male	183	1.000					
Female	75	1.252	0.683-2.293				
T status				<0.001			0.002
T1	138	1.000			1.000		
T2 or T3	120	8.932	4.043-19.730		3.849	1.613-9.184	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	6.583	3.588-12.079		3.111	1.608-6.019	
Systemic Inflammation Score				<0.001			0.036
0	171	1.000			1.000		
1, 2	87	2.810	1.661-4.754		1.784	1.039-3.063	
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.790	2.610-8.792				
Vascular invasion				<0.001			
Negative	154	1.000					
Positive	104	4.915	2.681-9.010				
Histological type				0.140			0.055
Intestinal	137	1.000			1.000		
Diffuse	121	1.489	0.877-2.529		1.690	0.989-2.890	
Postoperative complications				0.003			0.050
No	160	1.000			1.000		
Yes	98	2.273	1.334-3.873		1.709	0.999-2.924	

OR: Odds ratio; CI: confidence interval.

addition, the Low-SIS group showed significantly longer OS and RFS than the High-SIS group. Therefore, out results suggested that preoperative SIS may be a useful prognostic factor for patients with resectable gastric cancer.

The HR of SIS for gastric cancer in this study was 1.784 (95% CI=1.039-3.063, p=0.036). Prior studies have shown similar results. For example, Hara *et al*. evaluated the preoperative clinical impact of SIS in 138 gastric cancer patients undergoing curative treatment (12). They divided patients into an SIS-low group (n=45) and an SIS-high group (n=93) according to the preoperative SIS. The results showed that the 5-year OS rate was 86.6% in the SIS-low group and 66.6% in the SIS-High group (p=0.004). The 5-year RFS rate was 79.1% in the SIS-Low group, whereas it was 58.0% in the SIS-High group (p=0.007). The HR of the SIS was 2.143 (95%CI=1.126-4.078, p=0.020). Moreover, Lin *et al*. found the importance of preoperative SIS in patients undergoing radical resection of gastric cancer (13). They classified SIS into three groups, score 0 (n=781), score 1 (n=614), and score 2 (n=391). High SIS was associated with significantly higher local recurrence, peritoneal metastasis, and distant metastasis compared to low SIS (all p<0.001). Multivariate analysis also showed that SIS was associated with OS (SIS=1: HR=1.250, p=0.038; SIS=2: HR=1.728, p<0.001) and RFS (SIS=1: HR=1.248, p=0.055; SIS=2: HR=1.648, p<0.001). In addition, Inagaki *et al*. demonstrated the SIS accurately predicted the prognosis after the radical resection of gastric cancer (14). They categorized their study population into preoperative SIS 0 (n=955), SIS 1 (n=584), and SIS 2 (n=225) groups. They had assigned a cutoff value of 3.4 for the LMR. OS and RFS of patients in preoperative SIS 0, 1, and 2 groups became shorter with higher SIS (p<0.0001), identifying SIS 1 and 2 as independent prognostic factors (HR=1.35, 95%CI=1.06-1.272, p=0.0125 and HR=1.63, 95%CI=1.21-2.19, p=0.0012). Considering these findings, SIS is potentially useful as a prognostic predictor for resectable gastric cancer.

This study found that SIS was associated with OS and RFS in gastric cancer patients who underwent radical resection. There are some possible explanations for our findings. First, the SIS status was related to the introduction of adjuvant treatment after surgery. In the present study, the proportion of patients who required adjuvant chemotherapy

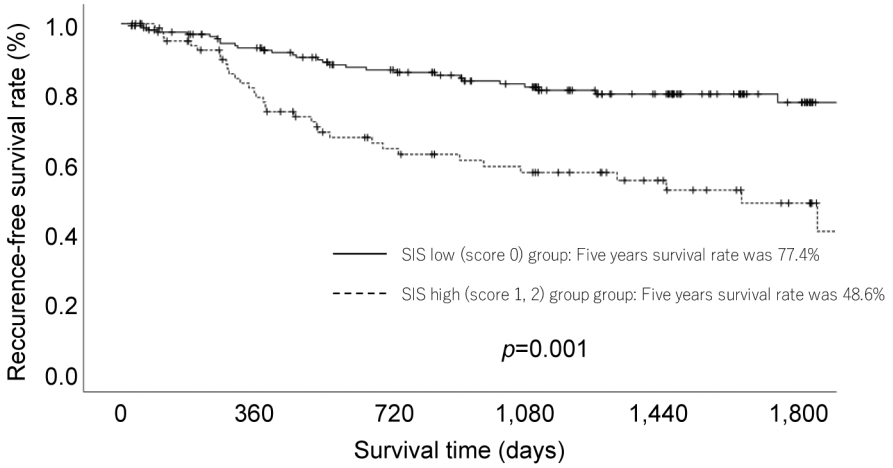

Figure 2. *Recurrence-free survival in the High-systemic inflammation score (SIS) and Low-SIS groups.*

Table III. *Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors for recurrence-free survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.008			
<75	179	1.000					
≥75	79	1.941	1.186-3.175				
Sex				0.301			
Male	183	1.000					
Female	75	1.347	0.766-2.370				
T status				<0.001			0.031
T1	138	1.000			1.000		
T2 or T3	120	7.642	3.892-15.005		2.395	1.081-5.305	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	7.642	4.333-13.476		3.458	1.813-6.518	
Systemic Inflammation Score				<0.001			0.039
0	171	1.000			1.000		
1, 2	87	2.913	1.787-4.750		1.710	1.027-2.847	
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.285	2.483-7.392				
Vascular invasion				<0.001			0.098
Negative	154	1.000			1.000		
Positive	104	5.112	2.935-8.903		1.757	0.902-3.422	
Histological type				0.368			0.099
Intestinal	137	1.000			1.000		
Diffuse	121	1.251	0.768-2.038		1.521	0.924-2.503	
Postoperative complications				0.001			0.015
No	160	1.000			1.000		
Yes	98	2.234	1.367-3.650		1.846	1.124-3.031	

OR: Odds ratio; CI: confidence interval.

was higher in the High-SIS group than that in the Low-SIS group. However, the introduction rate in the High-SIS group was lower than that in the Low-SIS. A similar result was observed in the previous study by Sato *et al*., which revealed that SIS is a simple predictor of the incidence of postoperative complications and survival in pT2-4 gastric

Table IV. *Patterns of recurrence according to the systemic inflammation score*.

	Systemic Inflammation Score				
	0 (n=171)		1, 2 (n=87)		*p*-Value
Recurrence site	Number	%	Number	%	
Peritoneal recurrence	15	8.8	14	16.1	0.078
Hematological recurrence	12	7.0	15	17.2	0.011
Lymph node recurrence	10	5.8	4	4.6	0.675
Local site	4	2.3	7	8.0	0.032

cancer patients (15). They categorized their patients into preoperative SIS 0 (n=78), SIS 1 (n=73), and SIS 2 (n=36) groups. The incidence of advanced cancer in the SIS 0, 1, and 2 groups was 78.2%, 79.5%, and 91.7%, respectively. Postoperative adjuvant chemotherapy for advanced cancer was administered to 73.8%, 55.2%, and 33.3% of the patients in the SIS 0, 1, and 2 groups, respectively, with patients with high SIS values showing lower rates. Taken together, the SIS status may have a clinical impact on the adjuvant chemotherapy course. Second, the SIS status was related to postoperative surgical complications. In the present study, the High-SIS group tended to have a higher rate of elderly patients, obese patients, and patients with diabetes mellitus, who are also known to have a higher risk of postoperative complications. In this study, although the complication rate did differ to a statistically significant extent according to the SIS, all patients for whom adjuvant chemotherapy could not be introduced had postoperative complications; this included 16 patients in the High-SIS group and 9 in the Low-SIS group, which amounted to a significant difference. A similar result was observed in a previous study: Sato *et al*. evaluated the clinical significance of preoperative SIS on short- and long-term prognosis in pT2-4 gastric cancer patients who underwent radical resection (15). They categorized their patients into preoperative SIS 0 (n=78), SIS 1 (n=73), and SIS 2 (n=36) groups. They clarified that there was a stepwise increase in the prevalence of postoperative complications in proportion to the SIS (p=0.043). In another study, Shoka *et al*. analyzed a multi-institutional dataset with the aim of identifying a predictor of post-gastrectomy pneumonia (16). They categorized their study population into preoperative SIS 0 (n=565), SIS 1 (n=586), and SIS 2 (n=264) groups. The prevalence of postoperative pneumonia gradually increased in parallel with the SIS, as did the overall complication rate (SIS 0, 20.4%; SIS 1, 20.8%, and SIS 2, 31.1%; p=0.001). Taken together, the SIS status was demonstrated to be correlated with the incidence of postoperative complications.

This study is accompanied by several limitations. First, it was a single-site study. Second, because it is retrospective, it may be subject to selection bias. Third, the mechanism of this study is not clarified. The interrelationships among nutritional status, immune status, and the dynamics of cytokines and related proteins need to be further evaluated. Despite these limitations, our study demonstrates that the preoperative SIS is a simple prognostic predictor for gastric cancer.

In conclusion, our study showed that the preoperative SIS could predict tumor recurrence and survival of gastric cancer patients and can help predict the long-term outcomes and determine the indications for postoperative adjuvant chemotherapy.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

MJ and TA made substantial contributions to the concept and design. MJ, TA, MF, TI, KK, KK2 (Keisuke Kazama), SS, HT, NY and YR made substantial contributions to the acquisition of data and their analysis and interpretation. MJ, TA, HT, NY and YR were involved in drafting the article or revising it critically for important intellectual content. MJ and TA gave their final approval of the version to be published.

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