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The Prognostic Value of the Perioperative Systemic Inflammation Score for Patients With Advanced Gastric Cancer

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Abstract. *Aim: We examined whether the perioperative systemic inflammation score (SIS), which describes systemic inflammation and/or malnutrition, affected the tumor recurrence and survival in advanced gastric cancer patients. Patients and Methods: The study retrospectively analyzed 160 patients with stage II/III gastric cancer who underwent curative resection at the Kanagawa Cancer Center. The SIS was evaluated before surgery, one week after surgery and one month after surgery, as determined by the serum albumin level (cut-off value=4.0 g/dl) and lymphocyte-to-monocyte ratio (cut-off value=4.44). Results: A high SIS at one month after surgery was identified as an independent predictor for overall survival [hazard ratio (HR)=2.143, p=0.020] and showed a marginal significance for the relapse-free survival (HR=1.814, p=0.053) in multivariate analyses. Conclusion: The SIS at one month after surgery is a useful biomarker for predicting the long-term outcome in patients with advanced gastric cancer.*

Gastric cancer is third-most frequent cause of cancer-related death worldwide (1), and prognosis is still unfavorable, especially in advanced gastric cancer, although the surgical procedures and perioperative treatment approaches have been improved over time (2-6).

Previous studies showed that systemic inflammation and/or malnutrition can affect long-term survival in patients with malignancies (7-9). Recently, the systemic inflammation score (SIS) was reported as a strong prognostic factor for renal cell carcinoma and colorectal cancer (10, 11). The preoperative SIS was also reported to be associated with the long-term outcome in patients with gastric cancer (12).

However, patients with gastric cancer are likely to develop postoperative systemic inflammation and/or malnutrition due to surgical stress, postoperative complications and difficulty achieving oral intake, which can affect tumor recurrence or compliance with adjuvant chemotherapy (13-16). Therefore, the postoperative SIS may affect the long-term survival in patients with gastric cancer, although this has not been reported. If the SIS after gastrectomy is indeed a prognosticator for patients with gastric cancer, we can improve the long-term outcomes of advanced gastric cancer patients through low-invasive surgery or nutritional intervention.

In the present study, we retrospectively evaluated the perioperative SIS and examined whether it affected the tumor recurrence and survival in patients who underwent curative resection for advanced gastric cancer.

Patients and Methods

The patients were retrospectively selected from the medical database of gastric cancer patients who underwent gastrectomy at the Department of Gastrointestinal Surgery of Kanagawa Cancer Center, according to the following criteria: 1) histologically proven common-type adenocarcinoma, according to the 15th edition of the Japanese Classification of Gastric Carcinoma (JCGC) published by the Japanese Gastric Cancer Association (JGCA) (17); 2) curative resection (R0 resection) with sufficient nodal dissection (D1+ or more) as a primary treatment between January 2008 and December 2013; 3) stage II or III disease diagnosed pathologically based on the 15th edition of JCGC and 4) available blood test results, including serum albumin (Alb) and white blood cell counts, in order to determine the SIS before surgery and one week and one month after surgery. The patients who were diagnosed with remnant gastric cancer, who had received preoperative chemotherapy and who had synchronous or metachronous other malignancies (within the past five years) were excluded.

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Key Words: Systemic inflammation score, gastric cancer, gastrectomy.

Surgery. The patients underwent total or subtotal gastrectomy with nodal dissection based on the Japanese gastric cancer treatment guidelines published by the JGCA (18). Conventional open gastrectomy and D2 lymph node dissection were performed as a standard treatment, but D1+ lymph node dissection was performed in patients with clinical T1N0 tumors, and laparoscopy-assisted gastrectomy was performed for patients with clinical stage I disease. Splenectomy was indicated for cases of advanced tumor located in the upper third of the stomach, but spleen preservation was performed for proximal gastric cancer not invading the greater curvature.

Perioperative care. We treated all patients with the common perioperative management based on the enhanced recovery after surgery (ERAS) protocol, which we have previously reported (19). The patients were permitted to eat until midnight on the day before surgery and were required to drink the contents of two 500-ml plastic bottles of oral rehydration solution by 3 h before surgery.

Surgery was performed under general anesthesia with epidural anesthesia. A continuous epidural infusion of analgesics was given until postoperative day (POD) 2, and a non-steroidal anti-inflammatory drug (NSAID) (50 mg flurbiprofen axetil) was administered intravenously twice daily after surgery until the resumption of oral intake. Oral intake was allowed on POD 2, starting with water. The patients started to eat solid food on POD 3, beginning with rice gruel and advancing in three steps to regular food on POD 7. The patients were allowed to be discharged from the hospital after POD 7 provided X-ray and blood examination findings were normal.

Adjuvant chemotherapy. The patients with pathological stage II or III disease, excluding T1N2-3 and T3N0 disease, received adjuvant chemotherapy with S-1 monotherapy or capecitabine plus oxaliplatin (XELOX) therapy (3, 4). In principle, adjuvant chemotherapy was started within six weeks after surgery. In S-1 monotherapy, S-1 was administered orally twice a day for four weeks followed by two weeks of rest, which was repeated for the first year after surgery. In XELOX therapy, oxaliplatin was given intravenously on the first day of a cycle, and capecitabin was administered orally twice a day for two weeks followed by one week of rest, which was repeated for the first six months after surgery.

SIS definition. The SIS was determined by the Alb level and lymphocyte-to-monocyte ratio (LMR). Based on the previous studies, the patients with Alb ≥4.0 g/dl and LMR ≥4.44 were defined as a score of 0, those with either Alb <4.0 g/dl or LMR <4.44 were defined as a score of 1, and those with Alb <4.0 g/dl and LMR <4.44 were defined as a score of 2. The SIS was calculated before surgery, at one week after surgery and at one month after surgery. The preoperative SIS was assessed within four days before the operation, and the SIS at one month after surgery was examined before starting adjuvant chemotherapy. We evaluated the proportion of SISs in each period. The patients were classified into two groups based on a low (score 0) or high (score 1 and 2) SIS at one month after surgery.

Evaluations. The pathological tumor depth, nodal status and staging were determined according to the JGCG 15th. Postoperative surgical complications were defined as those of Clavien-Dindo classification grade ≥2 occurring within 30 days after the operation (20). The patients were examined for at least five years after surgery by physical examinations, blood tests and chest-abdominal computed tomography or ultrasonography. The overall survival (OS) was defined as the period between surgery and the date of the patient's death from any cause or the date of the last follow-up. The relapse-free survival (RFS) was defined as the period between surgery and the date of either death, tumor recurrence or last follow-up.

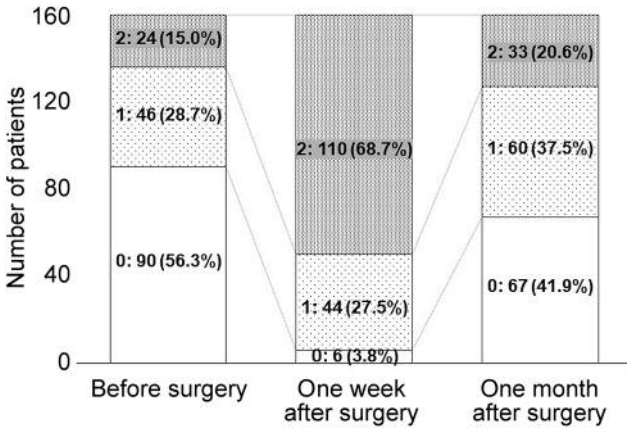

Figure 1. *The proportion of systemic inflammation score 0, 1, and 2 before surgery, at one week after surgery and at one month after surgery.*

Statistical analyses and ethics. A Chi-square test and Mann-Whitney *U*-test were performed to compare the patients in the low and high score of SIS at one month after surgery. The five-year OS and RFS rates were calculated by the Kaplan–Meier method, and a log rank test was performed to compare the two groups. Univariate and multivariate Cox proportional hazard models were developed to analyze the hazard ratio (HR) for the OS and RFS. Variables with *p*-values <0.05 in the univariate analysis were included in the multivariate analysis. For all tests, a 2-sided $p<0.05$ was considered significant.

Statistical analyses were performed using the SPSS Statistics software program, ver. 24 (IBM, Chicago, IL, USA). This study was approved by the Institutional Review Board of Kanagawa Cancer Center (No. 2018-127).

Results

Patient population. A total of 311 patients underwent gastrectomy for gastric cancer diagnosed as pathological stage II or III disease between January 2008 and December 2013 at our institute. Of these 311 patients, 160 were enrolled in the study, excluding 13 who were diagnosed with histological special type tumor, 13 who were remnant gastric cancer, 51 who received preoperative chemotherapy, 15 who had synchronous and metachronous malignancy in other organs, 11 who underwent non-curative resection (R1/2 resection) and 48 who did not have any available results for

perioperative Alb and/or white blood cell differentiation to determine the SIS.

Perioperative SIS. Figure 1 shows the proportions of SIS before surgery, at one week after surgery and at one month after surgery. A high SIS (1 or 2) was observed in 70 patients (43.7%) before surgery and 93 patients (58.1%) at one month after surgery, values that were relatively similar. In contrast, almost all patients (96.2%) showed a high SIS at one week after surgery.

Characteristics of patients with low and high SIS at one month after surgery. Table I shows the clinical and pathological characteristics of patients in the low and high SIS groups at one month after surgery. Regarding clinical characteristics, the patients in the high SIS group showed a significantly older age and worse American Society of Anesthesiologists-physical status (ASA-PS) and developed postoperative complications more frequently than those in the low SIS group. The pathological findings of patients, such as the pathological tumor depth, nodal status, lymph vascular invasion and stage, were not significantly different between the two groups.

Survival analyses. The Kaplan–Meier curves for the OS are shown in Figure 2. The 5-year OS rates after surgery were 86.6% and 66.6% in the low- and high-SIS groups, respectively, at one month after surgery, showing a significant difference (p=0.004). Table II shows the results of univariate and multivariate analyses for the OS. In the univariate analyses, the OS was associated with the type of surgery, pathological T factor and SIS at one month after surgery, so these factors were included in the multivariate analysis. A high SIS at one month after surgery was identified as an independent predictive factor for the OS [HR=2.143, 95% confidence interval (CI)= 1.126-4.078, p=0.020].

The Kaplan–Meier curves for the RFS are shown in Figure 3. The 5-year RFS rates after surgery were 79.1% and 58.0% in the low and high SIS groups, respective, at one month after surgery, showing a significant difference (p=0.007). Table III shows the results of univariate and multivariate analyses for the RFS. In the univariate analyses, the RFS was associated with the age, type of surgery, pathological T factor and SIS at one month after surgery, so these factors were included in the multivariate analysis. None of them were shown to be independent predictive factor for the RFS; however, there was marginal significance for a high SIS at one month after surgery (HR=1.814, 95% CI=0.993-3.315, p=0.053).

Initial recurrence site. Table IV shows the patterns of initial recurrence following gastrectomy in the low- and high-SIS groups at one month after surgery. Peritoneal recurrence was the most frequent in both groups. Hematological recurrence was significantly more frequent in the high-SIS group than in the low-SIS group (p=0.028). In contrast, the frequency of locoregional, lymph node and peritoneal recurrence was not markedly different between the two groups.

Discussion

The present study aimed to evaluate whether or not the perioperative SIS, a novel biomarker for systemic inflammation and/or malnutrition, affected the tumor recurrence and survival in patients who underwent curative resection for advanced gastric cancer. The major findings were that a high SIS at one month after surgery was an independent predictive factor for the OS and that hematological recurrence was significantly more frequent in the high-SIS group than in the low-SIS group at one month after surgery. The SIS at one month after surgery recovered nearly to its preoperative status, whereas the SIS at one week after surgery was quite high due to surgical stress. Our results suggest that prolonged systemic inflammation and/or malnutrition within one month after surgery might worsen the long-term outcome of patients with advanced gastric cancer.

Numerous reports have shown that systemic inflammation and nutritional status are associated with the long-term outcomes of patients with malignancy, including gastric cancer (7, 21). As an indicator of systemic inflammatory status, the ratios of peripheral blood cells, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and LMR, were identified as prognostic factors in patients with gastric cancer (22-26). Pan *et al*. reported that the LMR was the only hematological factor independently predicting a poor survival in a multivariate analysis (HR=1.49, 95% CI=1.17-1.89, p=0.01) when comparing these inflammatory markers in patients with resectable gastric cancer (25). Lymphocytes play an important role in inhibiting tumor cell proliferation, invasion and metastasis by enhancing anti-cancer immunity, which helps improve the outcomes of patients with malignancy (21, 27). In contrast, monocytes exert a positive influence on cancer progression, promoting tumor cell growth and survival, through tumor-monocyte-endothelial interaction (28-31). Patients with a low LMR, including lymphopenia and monocytosis, therefore tend to show a poor survival.

The Alb value describes not only the nutritional status, but also secondary changes in the systemic inflammatory response. Previous reports have shown that pretherapeutic hypoalbuminemia affects the long-term outcomes of patients with malignancy (32, 33). Furthermore, the Glasgow Prognostic Score (GPS), a scoring system that consists of Alb and C-reactive protein (CRP), is well recognized and has been standardized as a strong predictor of the survival of cancer patients (8, 9, 34). However, while CRP is a sensitive

Table I. *The relationship between clinicopathological characteristics and systemic inflammation score at one month after surgery.*

			SIS at one month				
	All cases		Low (score 0)		High (score 1-2)		
	Number	%	Number	%	Number	%	*p*-Value
Gender							0.446
Male	102	63.7	45	67.2	57	61.3	
Female	58	36.3	22	32.8	36	38.7	
Age (years old)							0.001
Median (range)	67 (24-86)		63 (24-84)		67 (29-86)		
BMI							0.996
Median (range)	22.2 (14.2-30.1)		22.2 (17.1-27.8)		22.3 (14.2-30.1)		
ASA-PS							<0.001
1	49	30.6	31	46.3	18	19.4	
2 or 3	111	39.4	36	53.7	75	80.6	
Resection							0.062
Subtotal gastrectomy	84	52.5	41	61.2	43	46.2	
Total gastrectomy	76	47.5	26	38.8	50	53.8	
Approach							0.119
Conventional	135	84.4	53	79.1	82	88.2	
Laparoscopy	25	15.6	14	20.9	11	11.8	
Lymph node dissection							0.680
D1+	31	19.4	14	20.9	17	18.3	
D2	129	80.6	53	79.1	76	81.7	
Operation time (min)							0.370
Median (range)	215 (116-554)		214 (116-398)		217 (116-554)		
Blood loss (ml)							0.082
Median (range)	235 (0-1,140)		230 (0-1,070)		275 (10-1,440)		
Postoperative complications (C-D>grade 2)							<0.001
No	130	81.3	64	95.5	66	71.1	
Yes	30	18.8	3	4.5	27	29.0	
Histological type							0.242
Differentiated type	61	38.1	22	32.8	39	41.9	
Undifferentiated type	99	61.9	45	67.2	54	58.1	
Pathological T factor (JCGC15th)							0.222
pT1	11	6.9	5	7.5	6	6.5	
pT2	32	20	18	26.9	14	15.1	
pT3	42	26.3	18	26.9	24	25.8	
pT4	75	46.9	26	38.8	49	52.7	
Pathological N factor (JCGC15th)							0.579
pN0	30	18.8	12	17.9	18	19.4	
pN1	38	23.8	14	20.9	24	25.8	
pN2	39	24.4	20	29.9	19	20.4	
pN3	53	33.1	21	31.3	32	34.4	
Lymph vascular invasion							0.682
Negative	29	18.1	11	16.4	18	19.4	
Positive	131	81.9	56	83.6	75	80.6	
Pathological stage (JCGC15th)							0.359
pStage II	72	45	33	49.3	39	41.9	
pStage III	88	55	34	50.7	54	58.1	
Postoperative chemotherapy							0.977
No	36	22.5	15	22.4	21	22.6	
Yes	124	77.5	52	77.6	72	77.4	

SIS, Postoperative one month-systemic inflammation score; ASA-PS, American Society of Anesthesiologists-physical status; C-D, Clavien-Dindo classification; JCGC, Japanese Classification of Gastric Carcinoma.

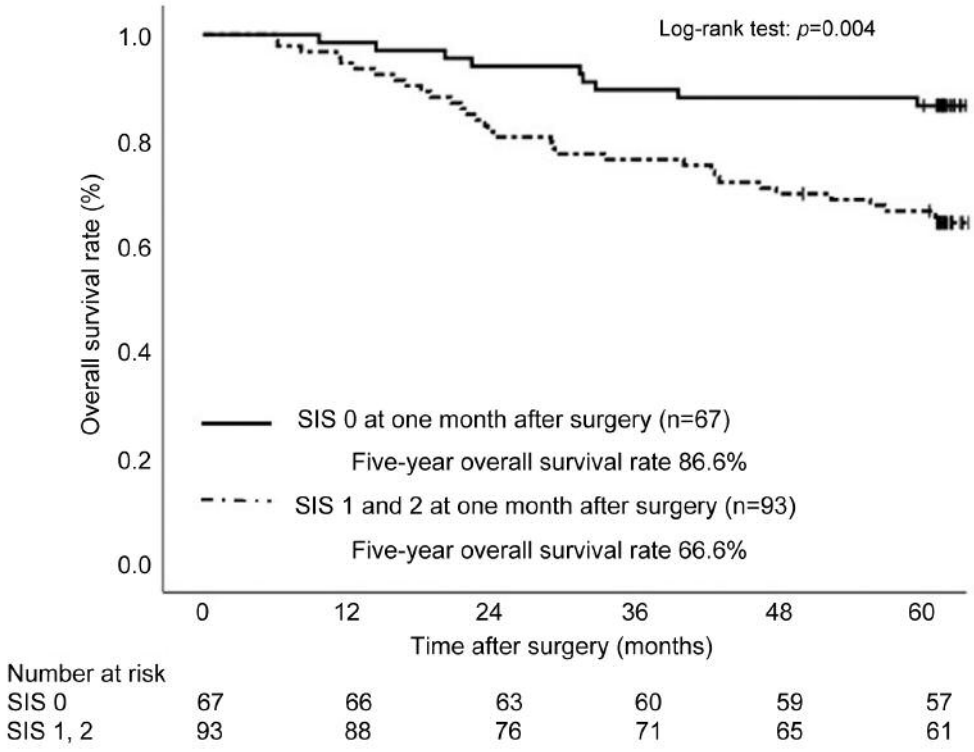

Figure 2. *The overall survival curves of the patients with low and high systemic inflammation scores at one month after surgery.*

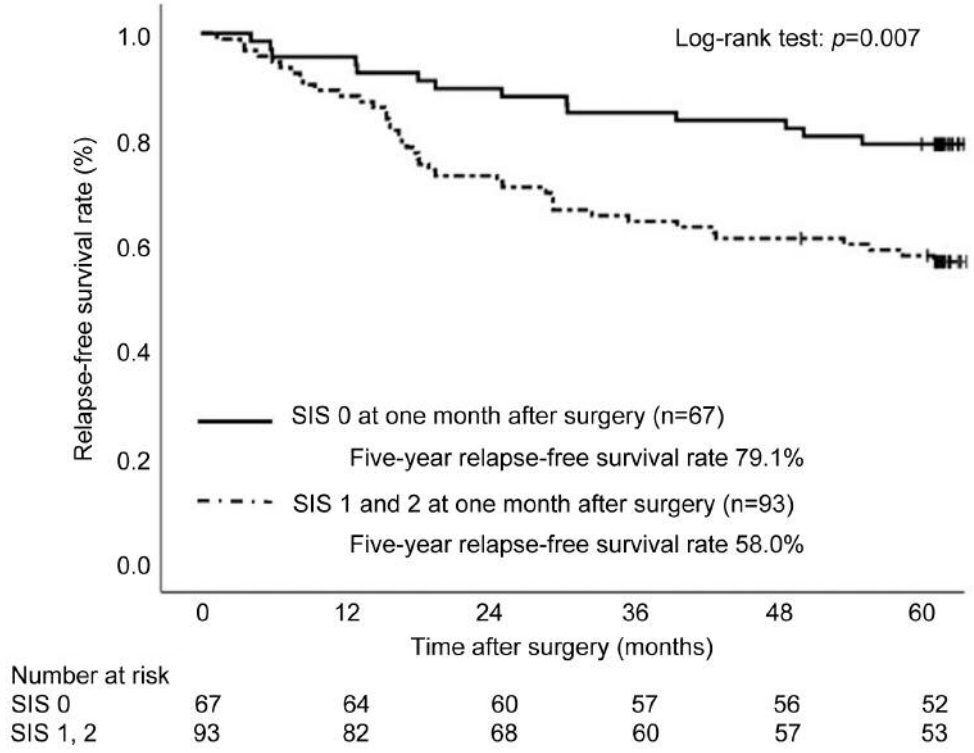

Figure 3. *The relapse-free survival curves of the patients with low and high systemic inflammation scores at one month after surgery.*

Table II. *Results of univariate and multivariate Cox proportional hazards analyses of the prognostic factors for the overall survival.*

		Univariate			Multivariate	
	N	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (years old)				0.081			
<65	58	1.000					
>65	102	1.763	0.933-3.334				
Type of gastrectomy				0.024			0.153
Subtotal gastrectomy	84	1.000			1.000		
Total gastrectomy	76	1.926	1.089-3.407		1.533	0.853-2.756	
Lymph node dissection				0.087			
D1+	31	1.000					
D2	129	0.574	0.304-1.084				
Postoperative complications (C-D>grade 2)				0.279			
No	130	1.000					
Yes	30	1.434	0.747-2.750				
Pathological T factor (JCGC15th)				0.028			0.153
pT1-2	43	1.000			1.000		
pT3-4	117	2.455	1.103-5.467		1.931	0.849-4.395	
Pathological N factor (JCGC15th)				0.172			
pN0	30	1.000					
pN1-3	130	1.814	0.771-4.269				
Lymph vascular invasion				0.500			
Negative	29	1.000					
Positive	131	1.319	0.590-2.945				
SIS at one month				0.006			0.020
Low (score 0)	67	1.000			1.000		
High (score 1, 2)	93	2.458	1.299-4.648		2.143	1.126-4.078	

HR, Hazard ratio; CI, confidence interval; C-D, Clavien-Dindo classification; JCGC, Japanese Classification of Gastric Carcinoma; SIS, systemic inflammation score.

marker for inflammation, it is not routinely measured before surgery or in the remote postoperative period in outpatient settings. Therefore, the SIS, which is the combination of LMR and Alb, is a more convenient and suitable biomarker for evaluating perioperative systemic inflammation and/or malnutrition in clinical practice than the GPS.

The present study showed that a high SIS at one month after surgery was associated with a poor survival in gastric cancer patients. Although most previous studies reported that the pretherapeutic inflammation and/or malnutrition status affected the long-term outcomes in patients with malignancy, only a few studies have shown postoperative changes in the inflammatory and/or malnutritional status to be related to the long-term survival (35-38). We, therefore, also analyzed whether or not the SIS before surgery or at one week after surgery affected the long-term outcome of the patients (data not shown). However, they were not found to be predictive factors for survival or tumor recurrence, suggesting that subacute or chronic systemic inflammation and/or malnutrition caused by surgical stress and postoperative events has a greater influence on the tumor recurrence and survival than the preoperative status in patients who undergo curative resection for advanced gastric cancer.

Postoperative complications, especially infectious complications, are well reported to adversely affect the long-term outcome of patients following curative gastrectomy (14, 39, 40), which is one possible explanation why the SIS at one month after surgery affected the long-term outcome. Furthermore, postoperative body weight loss due to surgical stress, postoperative complications and decreased oral intake can worsen the continuation of S-1 adjuvant chemotherapy and consequently the patient survival, that we previously reported (15, 16). For these reasons, postoperative subacute or chronic systemic inflammation and/or malnutrition can adversely affect the long-term survival in patients who undergo gastrectomy.

In the present study, the patients with a high SIS at one month after surgery were largely elderly with a poor ASA-PS and postoperative complications. Perioperative intervention should, therefore, be considered in these cases to improve their SIS after surgery and long-term survival. Low-invasive surgery can help reduce postoperative complications. We, therefore, need to plan gastrectomy carefully in terms of the surgical procedure, approach, degree of lymphadenectomy and combined resection of any other organ in order to avoid postoperative complications. Furthermore, nutritional therapy

Table III. *Results of univariate and multivariate Cox proportional hazards analyses of the prognostic factors for the relapse-free survival.*

		Univariate			Multivariate		
	N	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (years old)				0.042			0.308
<65	58	1.000			1.000		
>65	102	1.881	1.023-3.460		1.392	0.737-2.628	
Type of gastrectomy				0.011			0.083
Subtotal gastrectomy	84	1.000			1.000		
Total gastrectomy	76	2.010	1.173-3.442		1.633	0.937-2.844	
Lymph node dissection				0.336			
D1+	31	1.000					
D2	129	0.738	0.397-1.372				
Postoperative complications (C-D>grade 2)				0.097			
No	130	1.000					
Yes	30	1.650	0.913-2.983				
Pathological T factor (JCGC15th)				0.029			0.155
pT1-2	43	1.000			1.000		
pT3-4	117	2.213	1.084-4.517		1.704	0.817-3.556	
Pathological N factor (JCGC15th)				0.075			
pN0	30	1.000					
pN1-3	130	2.164	0.926-5.052				
Lymph vascular invasion				0.200			
Negative	29	1.000					
Positive	131	1.681	0.760-3.716				
SIS at one month				0.009			0.053
Low (score 0)	67	1.000			1.000		
High (score 1, 2)	93	2.183	1.219-3.910		1.814	0.993-3.315	

HR, Hazard ratio; CI, confidence interval; C-D, Clavien-Dindo classification; JCGC, Japanese Classification of Gastric Carcinoma; SIS, systemic inflammation score.

Table IV. *A comparison of the initial site of recurrence between the low and high systemic inflammation scores at one month after surgery.*

			SIS at one month				
	All cases		Low (score 0)		High (score 1-2)		
	Number	%	Number	%	Number	%	*p*-Value
Locoregional recurrence	4	2.5	1	1.5	3	3.2	0.442
Lymph node recurrence	13	8.1	4	6.0	9	9.7	0.397
Peritoneal recurrence	27	16.9	10	14.9	17	18.3	0.576
Hematological recurrence	14	8.8	2	3.0	12	12.9	0.028
Liver	2	1.3	0	0	2	2.2	0.336
Lung	6	3.8	1	1.5	5	5.4	0.200
Bone	4	2.5	0	0	4	4.3	0.111
Adrenal	2	1.3	1	1.5	1	1.1	0.664
Other	3	1.9	0	0	3	3.2	0.194

SIS, Systemic inflammation score.

is expected to improve the SIS at one month after surgery in high-risk patients. Imamura *et al*. reported that a postoperative oral elemental diet prevented postoperative weight loss at 6-8 weeks after gastrectomy in a randomized controlled, open-label, multi-center trial; however, they recruited only 112 patients and did not analyze the impact on the long-term survival (41). Ida *et al*. also conducted a randomized controlled clinical trial comparing standard diet with perioperative oral immunonutrition using an eicosapentaenoic acid-enriched supplement in patients who underwent total gastrectomy for

gastric cancer; however, they were unable to prove the efficacy of nutritional intervention for reducing body weight loss after surgery (42). Therefore, prospective large-scale trials are required to evaluate whether or not perioperative nutritional therapy can improve the long-term prognosis in patients who undergo gastrectomy for gastric cancer.

We also found that hematological recurrence was significantly more frequent in the high-SIS group than in the low-SIS group at one month after surgery. Sato *et al*. further reported that preoperative SIS was linked to the prevalence of hematogenous recurrence, and the proportions of patients with SIS 0, 1 and 2 were 6%, 10% and 19%, respectively (43). Although why the patients with a high SIS tended to experience hematological recurrence is unclear, these patients should receive careful observation and diagnostic imaging, such as computed tomography and/or ultrasonography, for the early detection of tumor recurrence after surgery.

There are advantages of using SIS at one month after surgery to predict tumor recurrence and survival of patients with advanced gastric cancer. First, Alb and LMR are measurable in the in-hospital laboratory at most institutions with a low-cost. Moreover, SIS at one month after surgery may help surgeons determine the indication for postoperative adjuvant chemotherapy, because the score is evaluated just before starting adjuvant chemotherapy and is able to predict long-term outcome of patients after gastrectomy. On the other hand, we need to mention several limitations associated with the present study. First, it was a retrospective, small-sized, single-center study. Furthermore, we cannot exclude the possibility of selection bias. There is the possibility that only patients with a good status were selected because our hospital is a regional cancer center that treats only cancer patients. In addition, patients with a severe surgical risk, such as elderly patients and those with a poor performance status and severe comorbidities, were unable to receive surgery in our Institute, as our Institute is a cancer-specific center and unable to treat postoperative cardiovascular and renal complications. These factors may have led to the postoperative SIS being better than in other reports. Second, the LMR cut-off value of 4.44 was determined in the first report of SIS, which investigated patients with renal cell carcinoma (10). Therefore, whether or not this cut-off value applies to patients with gastric cancer is unclear. Third, the study evaluated the SIS at one month after surgery; however, which period is optimal for evaluating the SIS after surgery in order to predict the long-term survival in patients with gastric cancer remains unclear. A large-scale study is required to identify the optimal cut-off value of the LMR for gastric cancer and optimal period for evaluating the SIS in order to estimate the long-term outcome.

However, despite the above-mentioned limitations, the present study is the first to evaluate both the preoperative and postoperative SIS and demonstrate that the SIS at one month after surgery can be a useful predictive marker for the tumor recurrence and survival in patients who receive curative resection for advanced gastric cancer.

In conclusion, our study showed that the SIS at one month after surgery could predict the tumor recurrence and survival of patients with advanced gastric cancer. The SIS at one month after surgery is a useful and reliable biomarker that can be measured with a low-cost and non-invasive examination and can help surgeons estimate the long-term outcomes and determine the indication for postoperative adjuvant chemotherapy.

Conflicts of Interest

The Authors have declared that no competing interests exist.

Authors' Contributions

Kentaro Hara and Toru Aoyama made substantial contributions to conception and design. Kentaro Hara, Takanobu Yamada, Masato Nakazono, Shinsuke Nagasawa, Yota Shimoda, Yuta Kumazu, Tsutomu Hayashi, Takashi Ogata and Takashi Oshima made substantial contributions to acquisition of data, or analysis and interpretation of data. Toru Aoyama, Takanobu Yamada, Masakatsu Numata, Tsutomu Hayashi, Hiroshi Tamagawa, Manabu Shiozawa, Soichiro Morinaga and Norio Yukawa have been involved in drafting the manuscript or revising it critically for important intellectual content. Yasushi Rino, Munetaka Masuda, Takashi Ogata and Takashi Oshima have given final approval of the version to be published. Each Author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Authors read and approved the final manuscript.

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