Title

Systemic Immune-Inflammation Index Predicts Overall Survival in Patients with Gastric Cancer: a Propensity Score-Matched Analysis

Author(s)

Noriyuki Hirahara, Yoshitsugu Tajima, Takeshi Matsubara, Yusuke Fujii, Shunsuke Kaji, Yasunari Kawabata, Ryoji Hyakudomi, Tetsu Yamamoto, Yuki Uchida, Takahito Taniura

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Authors: Noriyuki Hirahara, Yoshitsugu Tajima, Takeshi Matsubara, Yusuke Fujii, Shunsuke Kaji, Yasunari Kawabata, Ryoji Hyakudomi, Tetsu Yamamoto, Yuki Uchida, and Takahito Taniura

Affiliation: Department of Digestive and General Surgery, Shimane University Faculty of Medicine

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Corresponding author: Name: Noriyuki Hirahara

Department of Digestive and General Surgery, Shimane University Faculty of Medicine

89-1 Enya-cho, Izumo, Shimane 693-8501, Japan

Tel: +81-853-20-2232 Fax: +81-853-20-2229 E-mail: norinorihirahara@yahoo.co.jp

Co-authors' email addresses:

Yoshitsugu Tajima, email: ytajima@med.shimane-u.ac.jp

Takeshi Matsubara, email: nanadai@med.shimane-u.ac.jp

Yusuke Fujii, email: yuusuke@med.shimane-u.ac.jp

Shunsuke Kaji, email: s.kaji@med.shimane-u.ac.jp

Yasunari Kawabata, email: batayan5@med.shimane-u.ac.jp

Ryoji Hyakudomi, email: hyakuryo@med.shimane-u.ac.jp

Tetsu Yamamoto, email: t2t2@med.shimane-u.ac.jp

Yuki Uchida, email: yuchida@med.shimane-u.ac.jp

Takahito Taniura, email: taniura@med.shimane-u.ac.jp

Author Contributions

NH was the lead author, and conceived this study. TM, YK, YF, SK, TY, RH, YU and TT collected data, performed analysis, and drafted the manuscript. YT reviewed paper

and technique of surgery. All authors read and approved the final manuscript.

Abstract

Background

The systemic immune inflammation index (SII), integrated by peripheral lymphocyte, neutrophil, and platelet counts, is used as an objective biomarker that reflects the balance between host inflammatory and immune response status in cancer patients. Herein, we examined the prognostic significance of SII in gastric cancer patients.

Methods

We retrospectively reviewed data of 415 patients who underwent curative laparoscopic gastrectomy using propensity score-matched (PSM) analysis. The prognostic value of SII was compared between two groups based on SII values: low SII group (SII < 661.9) and high SII group (SII ≥ 661.9).

Results

In multivariate analysis, American Society of Anesthesiologists physical status (ASA-PS) (p<0.001), tumor differentiation (p=0.019), pathological stage (p=0.046), carcinoembryonic antigen (CEA) level (p<0.001), SII (p=0.006), and operative procedure (p=0.009) were independent prognostic factors of overall survival (OS) in the overall PSM cohort. The log-rank test demonstrated that patients with a high SII had

significantly worse OS than did those with low SII (p=0.002).

In age-stratified subgroups analysis (<65/≥65 years), multivariate analysis revealed that ASA-PS (p<0.001), tumor differentiation (p=0.019), CEA level (p=0.008), SII (p=0.013), and operative procedure (p=0.026) were independent prognostic factors of OS in the elderly group. Similarly, elderly patients with a high SII had significantly worse OS than did those with a low SII (p=0.009).

Meanwhile, SII was not an independent prognostic factor of OS, and no significant association was observed between SII and OS in non-elderly patients.

Conclusions

SII was an independent prognostic indicator in gastric cancer patients, especially in the elderly population.

Key words: gastric cancer, systemic immune-inflammation index, overall survival

Introduction

Tumor-related systemic inflammation plays a crucial role in the development and metastasis of tumor cells by shielding circulating tumor cells from immune system recognition and subsequent destruction [1,2]. In addition, systemic immune-inflammatory response has been generally considered to affect cancer microenvironment that enables tumor cell proliferation, invasion, and migration and decreases in response to anticancer agents [3].

Previous studies have revealed that several inflammation-related biomarkers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), where the NLR and PLR comprise two types of inflammatory cells, were associated with cancer cell behavior and patient survival [4,5]. The systemic immune inflammation index (SII), a novel immunonutritional biomarker integrated by the peripheral lymphocyte, neutrophil, and platelet counts, has recently been a more objective and attractive biomarker that reflects the balance between host inflammatory and immune response status in patients with various types of cancer [6].

Gastric cancer, one of the most common malignant tumors of the digestive tract, is the major leading cause of cancer-related death worldwide [7]. Despite improvements in early detection, surgical treatment, chemotherapy, and molecular targeted therapy, the

prognosis has been unfavorable over the past decade [8]. In addition, a heterogeneous clinical course is frequently observed even among gastric cancer patients with the same pathological stage or age population. Further studies are thus needed to identify more specific and sensitive prognostic biomarkers that enable us to predict prognosis, select patients with the worst prognosis, and determine optimal individualized therapeutic strategies.

To our knowledge, few previous studies have addressed the role of SII in gastric cancer. In the present study, we examined the prognostic significance of SII in patients with gastric cancer.

Materials and Methods

Patients

We retrospectively reviewed medical records of 415 consecutive patients who underwent curative laparoscopic gastrectomy with R0 resection for histologically confirmed gastric adenocarcinoma between January 2010 and December 2017 at our institution. R0 resection was defined as complete resection without any microscopic margin involvement. Exclusion criteria included active infection occurring within a month before surgery and chronic systemic inflammatory or autoimmune diseases. In

addition, patients who received neoadjuvant chemotherapy were excluded.

The extent of gastric resection and lymph node dissection was determined in accordance with the Japanese Gastric Cancer Treatment Guidelines (version 4) [9]. Pathological classification was performed according to the International Union Against Cancer Tumor, Node, Metastasis (TNM) classification (seventh edition) [10]. The need for informed consent was waived owing to the retrospective nature of the study.

To evaluate the effect of each clinical variable on the patient's prognosis with high confidence and to minimize biasing effects of confounders, propensity score matching (PSM) statistical analysis was performed on the following variables: depth of tumor, lymph node metastasis, and pTNM stage.

The protocol of this retrospective study was approved by the Ethical Review Board of Shimane University, Faculty of Medicine (Shimane, Japan), and the study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030472).

Blood analysis

Baseline data, including routine blood test, tumor marker, and clinicopathological findings, were retrospectively extracted from each patient's medical record. Patients

with full laboratory data on preoperative complete blood count (CBC) and blood differential data were enrolled in the study. These data were derived within 7 days before surgery. CBC was analyzed using an automated hematology analyzer XE-5000 (SYSMEX K1000 hematology analyzer; Medical Electronics. Kobe, Japan).

SII was calculated based on platelet (P; $\times 10^9$/l), granulocyte as a proxy for neutrophils (N; $\times 10^9$/l), and lymphocyte (L; $\times 10^9$/l) blood counts using the following formula: SII = P × N/L. Using receiver operating characteristic (ROC) curve analysis, an accurate SII cut-off value of 661.9 (sensitivity, 40.9%; specificity, 78.9%; area under the curve=0.584) was determined to verify the optimal cut-off value of preoperative SII for predicting overall survival (OS) (Fig. 1), and thus, patients were categorized into two groups based on SII values; a low SII group (SII < 661.9) and a high SII group (SII ≥ 661.9).

Follow-up analysis

Patients were carefully followed up every 3 months for 2 years and then every 6 months for 3–5 years after the surgery. OS was calculated from the date of surgical resection to the date of death from any cause or the date of the last follow-up.

Postoperative complications were evaluated according to the Clavien-Dindo

classification, and serious complications were defined as grade II or higher [11]. Postoperative complications after laparoscopic gastrectomy included surgical site infection, anastomotic leakage, pancreatic fistula, intra-abdominal abscess, and pneumonia.

Statistical analysis

Differences between categorical variables were evaluated using the Chi-squared test or Fisher's exact test. OS was plotted using the Kaplan-Meier method, and differences between survival curves were evaluated using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model, and hazard ratios (HRs) were calculated. Variables with a p-value <0.05 following univariate analyses were subsequently included in the multivariate logistic regression analysis. All statistical analyses were performed using the JMP software (version 14 for Windows; SAS Institute); p-values <0.05 were defined as statistically significant.

Results

Relationships between SII and clinicopathological features

Based on the SII cut-off value of 661.9 for OS, 309 (74.5%) and 106 (25.5%) patients were classified as having low and high SII, respectively.

As shown in Table 1, there were significant associations between SII and several clinicopathological factors such as age (p=0.025), the American Society of Anesthesiologists physical status (ASA-PS) classification (p<0.001), body mass index (BMI) (p=0.036), white blood cell count (p<0.001), neutrophil count (p<0.001), lymphocyte count (p<0.001), platelet count (p<0.001), tumor size (p=0.001), depth of tumor (p<0.001), lymph node metastasis (p=0.041), pathological stage (p<0.001), and C-reactive protein (CRP) level (p<0.001).

PSM stratification adequately balanced the distribution of the confounding variables (depth of tumor, lymph node metastasis, and pTNM stage) between the two groups, resulting in 106 identified matched pairs that were used for subsequent analyses (Table 1).

Cox regression analysis of OS in the PSM cohort

In univariate analysis, older age (p=0.049), poor ASA-PS (p<0.001), large tumor size (p=0.001), poor differentiation (p=0.024), advanced pathological stage (p<0.001), high carcinoembryonic antigen (CEA) level (p<0.001), high CRP level (p=0.008), high

SII (p=0.002), and laparoscopic total gastrectomy (p=0.002) were significantly associated with worse OS. Meanwhile, multivariate analysis revealed that ASA-PS (HR, 3.989; 95 % confidence interval [CI], 2.037–7.812; p<0.001), tumor differentiation (HR, 1.981; 95% CI, 1.118–3.509; p=0.019), pathological stage (HR, 1.809; 95% CI, 1.011–3.237; p=0.046), CEA level (HR, 2.463; 95% CI, 1.444–4.202; p<0.001), SII (HR, 2.189; 95% CI, 1.254–3.823; p=0.006), and operative procedure (HR, 2.104; 95% CI, 1.200–3.689; p=0.009) were independent prognostic factors of OS in the PSM cohort (Table 2).

Relationships between SII and clinicopathological features in age-stratified patients

Based on their age, 56 patients (26.4 %) were classified as the non-elderly group (aged <65 years) and 156 patients (73.6 %) as the elderly group (aged ≥65 years).

In the non-elderly group, 32 patients (57.1 %) had low SII, while the remaining 24 patients (42.9 %) had high SII. In the elderly group, 74 patients (47.4 %) were classified as the low SII group and the remaining 82 patients (52.6 %) as the high SII group.

197 Depth of tumor, lymph node metastasis, and pathological stage did not differ
198 significantly between the low and high SII groups in the age-stratified analysis (Table
199 3).
200
201 **Cox regression analysis of OS in age-stratified patients**
202 In the non-elderly group, univariate analysis identified advanced pathological stage
203 (p=0.003), high CRP level (p=0.025), laparoscopic total gastrectomy (p=0.038), and
204 adjuvant chemotherapy administration (p=0.033) to be significantly associated with
205 worse OS. In multivariate analysis, pathological stage (HR, 9.247; 95% CI, 0.790–
206 108.265; p=0.034) and CRP level (HR, 4.944; 95% CI, 1.238–19.740; p=0.024) were
207 independent prognostic factors of OS (Table 4).
208 On univariate analysis of the elderly group, poor ASA-PS (p<0.001), large tumor
209 size (p=0.012), poor differentiation (p=0.010), advanced pathological stage (p=0.010),
210 high CEA level (p<0.001), high SII (p=0.011), laparoscopic total gastrectomy
211 (p=0.011), and occurrence of postoperative complications (p=0.044) were significantly
212 associated with worse OS. Meanwhile, multivariate analysis revealed that ASA-PS (HR,
213 4.884; 95 % CI, 2.411–9.870; p<0.001), tumor differentiation (HR, 2.050; 95% CI,
214 1.125–3.738; p=0.019), CEA level (HR, 2.226; 95% CI, 1.236–4.006; p=0.008), SII

(HR, 2.177; 95% CI, 1.182–4.011; p=0.013), and operative procedure (HR, 2.044; 95% CI, 1.088–3.841; p=0.026) were independent prognostic factors of OS.

Association of OS with SII

The 5-year OS rates were 73.8 % and 54.8 % in patients with low and high SII, respectively. The log-rank test demonstrated that patients with high SII had significantly worse prognosis in terms of OS than did those with low SII (p=0.002) (Fig. 2).

Further analysis of the prognostic value of SII in the age-stratified subgroups showed that patients with high SII were associated with significantly worse OS than those with low SII (p=0.009) in the elderly group. The 5-year OS rates in patients with low and high SII were 69.0 % and 50.2 %, respectively. In the non-elderly patient group, however, no significant association was observed between SII and OS (Figs. 3a, 3b).

Discussion

Systemic immunoinflammatory parameters have been previously evaluated as candidates for predicting survival in various malignancies because systemic inflammation is considered as an effect rather than a cause of cancer [12-14]. The SII, integrated by peripheral lymphocyte, neutrophil, and platelet counts, has recently been considered as a more accurate and objective prognostic biomarker in several cancers because SII reflects the balance between host inflammatory and immune response status in cancer patients [15-17]. However, to our knowledge, the significance of SII in gastric cancer has not been evaluated. In this study, the prognostic significance of SII was examined in patients with gastric cancer who underwent curative resection. In addition, PSM analysis was performed to minimize the effects of confounding variables, such as depth of tumor, lymph node metastasis, and pTNM stage, on survival.

Neutrophils regulate tumor microenvironment by producing numerous inflammatory factors, such as vascular endothelial growth factor, matrix metalloproteinase-9, and anti-apoptotic factor (nuclear factor-κB), which promote tumor proliferation, progression, and metastasis. In addition, increased levels of neutrophils can release a large amount of nitric oxide, arginase, and reactive oxygen species (ROS), leading to disorders of T-cell activation. ROS released from neutrophils not only reduces the adhesion of extracellular

matrix but also inhibits apoptosis in tumor cells. Therefore, neutrophils may contribute to tumor growth and metastasis [18,19].

Lymphocytes exert an anti-tumor immune response by inducing cytotoxic cell death and by inhibiting cancer proliferation and migration via their ability to specifically target and kill cancer cells. In addition, lymphocytes release several types of cytokines such as interferon and TNF-α, which can control tumor cell growth and metastasis, thus improving prognosis in cancer patients. Therefore, lymphocytes can eliminate tumor cells through cellular and humoral immune mechanisms [20].

Platelets directly interact with cancer cells and secrete several growth factors, such as angiogenesis regulators and adhesive glycoproteins, which assist tumor cells in metastasizing to distant sites by enabling epithelial–mesenchymal transition [21]. Platelets can also create a defensive barrier around tumor cells in the circulation and protect circulating tumor cells from the host's immune surveillance.

Considering these facts, it would be logically conceivable that individuals with increased levels of neutrophils and platelets and/or a decreased level of lymphocytes are at a higher risk of cancer progression. In this study, we investigated the relationships between SII and various clinicopathological features, and high SII was significantly associated with advanced tumor-depth (p<0.001), lymph node metastasis (p=0.041), and

pathological stage (p<0.001). These results suggest that high SII could be used as an indicator of cancer progression in gastric cancer.

CRP, an acute-phase inflammatory protein, is one of the most frequently used serum biomarkers to evaluate cancer prognosis; however, it lacks specificity and could be elevated in a number of systemic stresses, such as infection, surgery, and connective tissue disease [22,23]. SII is considered a more reliable and objective indicator of cancer prognosis than CRP because it reflects the balance of host inflammatory and immune status. As expected, gastric cancer patients with high SII had significantly worse prognosis than did those with low SII (p=0.002). In addition, SII was an independent prognostic factor of OS in the PSM analysis for the whole cohort (p=0.006) and the elderly patients' cohort (p=0.013) in this study. Meanwhile, SII was not an independent prognostic factor in the non-elderly patient cohort. Elderly people are more likely to have inflammation and immunodeficiency associated with cancer, and SII may have been an indicator of OS because of the possibility of developing an immunodeficient state with aging, regardless of the presence of cancer [24-27]. However, non-elderly patients (especially those with non-advanced cancers) were not immunodeficient; therefore, SII lacked the power and was not a prognostic indicator [28]. Although a few reports have suggested that SII is a prognostic biomarker in several cancers and examined differences

283 in response to chemotherapy according to SII value, no study has conducted sub-analysis
284 in the elderly and non-elderly populations [29-32]. In the context of the currently aging
285 society, the novelty of this study is that we examined the significance of SII as an
286 independent predictive factor using age-stratified analysis.

287 The present study had some limitations. First, there were no consensual cut-off values
288 for most inflammation indices, including the SII. Individual cut-off levels have been
289 determined based on their relevance and significance in most previous studies. As a result,
290 there is a wide range of cut-off values that exist for SII [15-17, 33]. Before adopting SII
291 in routine practice, a universal cut-off value for SII should be verified in prospective and
292 well-designed randomized controlled trials. Second, we focused on the impact of
293 preoperative SII on survival after curative laparoscopic gastrectomy for gastric cancer,
294 but we failed to evaluate dynamic changes in SII during the postoperative period. Third,
295 nutritional indicators were not adequately assessed. Because previous studies have
296 reported that malnutritional status results in reduced neutrophil migration, decreased
297 lymphocyte count, and decreased function, further studies should be conducted to assess
298 the relationship among inflammation, immunity, and nutritional status [34,35]. Another
299 limitation was that some other well-known systemic inflammatory parameters, such as
300 tumor necrosis factor-α and interleukins, were not examined in this study owing to high

costs and inconvenience associated with such tests.

Conclusion

This study highlighted the importance of SII as an independent prognostic indicator in gastric cancer patients, especially in the elderly population, suggesting that patients with high SII should be carefully followed. Future multi-institutional prospective validation of our findings is desirable to examine the indications for adjuvant therapy based on SII values and implement SII as a valuable predictive biomarker in clinical practice.

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Figure and table legends

Fig. 1 Receiver operating curve for overall survival was plotted to verify the optimum cut-off value of SII score.

Fig. 2 Overall survival based on SII in propensity score matched 212 gastric cancer patients.

Fig. 3 Postoperative overall survival based on SII in age-stratified gastric cancer patients (a) non-elderly patients, (b) elderly patients.

Table 1. Relationships between SII values and clinicopathological features before and after propensity score matching

Table 2. Univariate and multivariate analyses for overall survival in propensity score-matched gastric cancer patients.

Table 3. Relationships between SII and clinicopathological features in age-stratified

gastric cancer patients

Table 4. Univariate and multivariate analyses for overall survival in age-stratified gastric cancer patients

Table 1. Relationships between SII values and clinicopathological features before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	Total patients	SII			Total patients	SII		
		< 661.9 (n=309)	≥ 661.9 (n=106)	*p* value		< 661.9 (n=106)	≥ 661.9 (n=106)	*p* value
Age (years)		70 (36-91)	74 (43-90)	0.025		72 (41-89)	74 (43-90)	0.101
Gender				0.593				0.758
Male	289	213	76		154	78	76	
Female	126	96	30		58	28	30	
ASA-PS				<0.001				0.008
1	24	20	4		9	5	4	
2	351	270	81		176	95	81	
3	40	19	21		27	6	21	
BMI		22.5 (14.7-40.4)	21.8 (14.0-32.5)	0.036		23.4 (16.9-30.5)	21.8 (14.0-32.5)	0.011
WBC		5530 (510-9280)	6495 (3510-13700)	<0.001		5615 (2870-8920)	6495 (3510-13700)	<0.001
Neutrophil		3160 (250-6190)	4530 (2650-11460)	<0.001		3200 (1450-5770)	4530 (2650-11460)	<0.001
Lymphocyte		1750 (230-3780)	1215 (230-2500)	<0.001		1815 (800-3780)	1215 (230-2500)	<0.001
Platelet		205 (36-460)	252 (119-726)	<0.001		218 (80-336)	252 (119-726)	<0.001
Location of tumor				0.717				0.475
EGJ	12	8	4			3	4	
U	81	63	18			25	18	
M	175	132	43			46	43	
L	147	106	41			32	41	
Operative procedure				0.247				0.493
LTG	88	63	25			27	25	
LPG	44	37	7			11	7	
L(A)DG	283	209	74			67	74	
Tumor size (mm)		40 (3-180)	50 (5-170)	0.001		44 (5-180)	50 (5-170)	0.401
Differentiation				0.262				0.279
Well	82	66	16		27	11	16	
Moderate	154	109	45		84	39	45	
Poor	179	134	45		101	56	45	
Depth of tumor				<0.001				0.998
T1a-1b	218	180	38		76	38	38	
2	56	43	13		26	13	13	
3	60	38	22		43	21	22	
4a-4b	81	48	33		67	34	33	
Lymph node metastasis				0.041				0.998
N0	276	216	60		119	59	60	
N1	51	37	14		28	14	14	
N2	45	27	18		37	19	18	
N3	43	29	14		28	14	14	
Pathological stage				<0.001				1.000
1a-1b	248	203	45		90	45	45	
2a-2b	75	51	24		48	24	24	
3a-3c	92	55	37		74	37	37	
CEA antigen (ng/ml)		3.2 (0.7-106.0)	3.6 (0.8-163.3)	0.147		3.2 (0.7-84.7)	3.6 (0.8-163.3)	0.493
CRP (mg/l)		0.07 (0.01-6.31)	0.16 (0.01-11.10)	<0.001		0.08 (0.01-5.35)	0.16 (0.01-11.10)	0.002
Postoperative complications				0.120				0.381
Absent		223	68			32	38	
Present		86	38			72	68	
Adjuvant chemotherapy				0.138				0.157
Yes	114	79	35		80	45	35	
No	301	230	71		132	61	71	

Table 2. Univariate and multivariate analyses for overall survival in propensity score-matched gastric cancer patients

Variables	Patients (n=212)	Category or characteristics	Univariate analysis			Multivariate analysis		
			HR	95%CI	p value	HR	95%CI	p value
Age	56/156	(<65/≥65)	1.979	1.003-3.905	0.049	1403	0.696-2.829	0.343
Gender	58/154	(female/male)	1.031	0.587-1.809	0.916			
BMI	190/22	(>18.5/<18.5)	1.285	0.609-2.713	0.511			
ASA	185/27	(<3/≥3)	4.688	2.553-8.609	<0.001	3.989	2.037-7.812	<0.001
Tumor size	106/106	(<5/≥5)	2.442	1.416-4.211	0.001	1.716	0.905-3.252	0.098
Diff.	111/101	(well & mod/poor)	1.839	1.084-3.119	0.024	1.981	1.118-3.509	0.019
pStage	138/74	(1,2/3)	2.829	1.692-4.731	<0.001	1.809	1.011-3.237	0.046
CEA	158/54	(<5.0/≥5.0)	2.556	1.522-4.294	<0.001	2.463	1.444-4.202	<0.001
CRP	171/41	(<0.5/>0.5)	2.088	1.211-3.600	0.008	1.345	0.711-2.546	0.362
SII	106/106	(<661.9/≥661.9)	2.292	1.342-3.915	0.002	2.189	1.254-3.823	0.006
Operative procedure	159/53	(Proximal & Distal / Total)	2.321	1.377-3.912	0.002	2.104	1.200-3.689	0.009
Postoperative complications	142/70	(absent/present)	1.657	0.988-2.781	0.056			
Adjuvant	132/80	(No/Yes)	1.25	0.751-2.082	0.391			

Table 3. Relationships between SII and clinicopathological features in age-stratified gastric cancer patients

Characteristics	Non-elderly patients				Elderly patients			
	Total patients	SII			Total patients	SII		
		< 661.9 (n=32)	≥ 661.9 (n=24)	p value		< 661.9 (n=74)	≥ 661.9 (n=82)	p value
Age (years)		59 (41-64)	61 (43-64)	0.131		77 (65-89)	77 (65-90)	0.441
Gender				0.533				0.505
Male	154	23	19		154	55	57	
Female	58	9	5		58	19	25	
ASA				0.121				0.054
1	5	3	2		4	2	2	
2	48	29	19		128	66	62	
3	3	0	3		24	6	18	
BMI		23.4 (16.9-29.8)	20.9 (14.0-32.5)	0.032		23.4 (17.6-30.5)	22.2 (15.4-29.8)	0.085
WBC		5840 (3610-8320)	6755 (4880-9180)	0.009		5555 (2870-8920)	6420 (3510-13700)	<0.001
Lymphocyte		1950 (1130-3250)	1320 (530-2500)	<0.001		1740 (800-3780)	1170 (230-2270)	<0.001
Neutrophil		3151 (2010-5720)	4775 (3120-6970)	<0.001		3218 (1450-5770)	4440 (2650-11460)	<0.001
Platelet		240 (147-336)	289 (141-543)	<0.001		199 (80-331)	244 (119-726)	<0.001
Location of tumor								0.775
EGJ	1	1	0	0.290	6	2	4	
U	13	9	4		30	16	14	
M	25	15	10		64	31	33	
L	17	7	10		56	25	31	
Operative procedure				0.340				0.884
LTG		9	4			19	21	
LPG		5	2			6	5	
L(A)DG		18	18			49	56	
Tumor size (mm)		41 (10-150)	42.5 (12-120)	0.389		50 (5-180)	52 (5-170)	0.795
Differentiation				0.929				0.283
Well	6	3	3		21	8	13	
Moderate	17	10	7		67	29	38	
Poor	33	9	14		68	37	31	
Depth of tumor				0.517				0.740
T1a-1b	26	15	11		50	23	27	
2	5	3	2		21	10	11	
3	11	8	3		32	13	19	
4a-4b	14	6	8		53	28	25	
Lymph node metastasis				0.490				0.720
N0	35	22	13		84	37	47	
N1	5	2	3		23	12	11	
N2	8	3	5		29	16	13	
N3	8	5	3		20	9	11	
Pathological stage				0.414				0.669
1a-1b	28	18	10		62	27	35	
2a-2b	12	5	7		36	19	17	
3a-3c	16	9	7		58	28	30	
CEA antigen (ng/ml)		2.8 (0.7-84.7)	3.0 (1.2-8.3)	0.842		3.35 (1.2-76.3)	3.65 (0.8-163.3)	0.434
CRP (mg/l)		0.06 (0.01-0.92)	0.11 (0.01-2.50)	0.002		0.09 (0.01-5.35)	0.18 (0.01-11.10)	0.008
Postoperative complications				0.338				0.715
Absent	41	25	16		101	49	52	
Present	15	7	8		55	25	30	
Adjuvant chemotherapy				0.440				0.047
Yes	27	14	13		53	31	22	
No	29	18	11		103	43	60	

Table 4. Univariate and multivariate analyses for overall survival in age-stratified gastric cancer patients

Variables	Non-elderly patients								Elderly patients						
	Patients (n=56)	Category or characteristics	Univariate analysis			Multivariate analysis			Patients (n=156)	Univariate analysis			Multivariate analysis		
			HR	95%CI	p value	HR	95%CI	p value		HR	95%CI	p value	HR	95%CI	p value
Gender	14/42	(female/male)	3.178	0.400-25.247	0.274				44/112	0.904	0.498-1.640	0.740			
BMI	51/5	(>18.5/<18.5)	2.386	0.504-11.288	0.273				139/17	1.109	0.471-2.611	0.813			
ASA	53/3	(<3/≥3)	5.483	0.599-50.178	0.132				132/24	4.184	2.207-7.932	<0.001	4.884	2.411-9.870	<0.001
Tumor size	34/22	(<5/≥5)	3.663	0.942-14.251	0.061				72/84	2.153	1.186-3.908	0.012	1.890	0.940-3.803	0.074
Diff.	23/33	(well & mod/poor)	1.153	0.318-4.176	0.828				88/68	2.152	1.205-3.845	0.01	2.050	1.125-3.738	0.019
pStage	40/16	(1,2/3)	11.159	2.337-53.270	0.003	9.247	0.790-108.265	0.034	98/58	2.09	1.198-3.646	0.01	1.252	0.655-2.393	0.497
CEA	46/10	(<5.0/≥5.0)	1.493	0.385-5.794	0.563				112/44	2.745	1.556-4.843	<0.001	2.226	1.236-4.006	0.008
CRP	48/8	(<0.5/>0.5)	4.572	1.214-17.220	0.025	4.944	1.238-19.740	0.024	123/33	1.721	0.938-3.156	0.08			
SII	32/24	(<661.9/≥661.9)	2.301	0.649-8.162	0.197				74/82	2.16	1.195-3.905	0.011	2.177	1.182-4.011	0.013
Operative procedure	43/13	(Proximal & Distal / Total)	3.743	1.076-13.026	0.038	2.703	0.659-11.090	0.167	116/40	2.116	1.186-3.778	0.011	2.044	1.088-3.841	0.026
Postoperative complications	41/15	(absent/present)	0.799	0.168-3.788	0.777				101/55	1.781	1.015-3.126	0.044	1.541	0.835-2.843	0.167
Adjuvant	29/27	(No/Yes)	5.786	1.155-28.992	0.033	1.176	0.102-13.567	0.896	103/53	1.01	0.570-1.789	0.973			

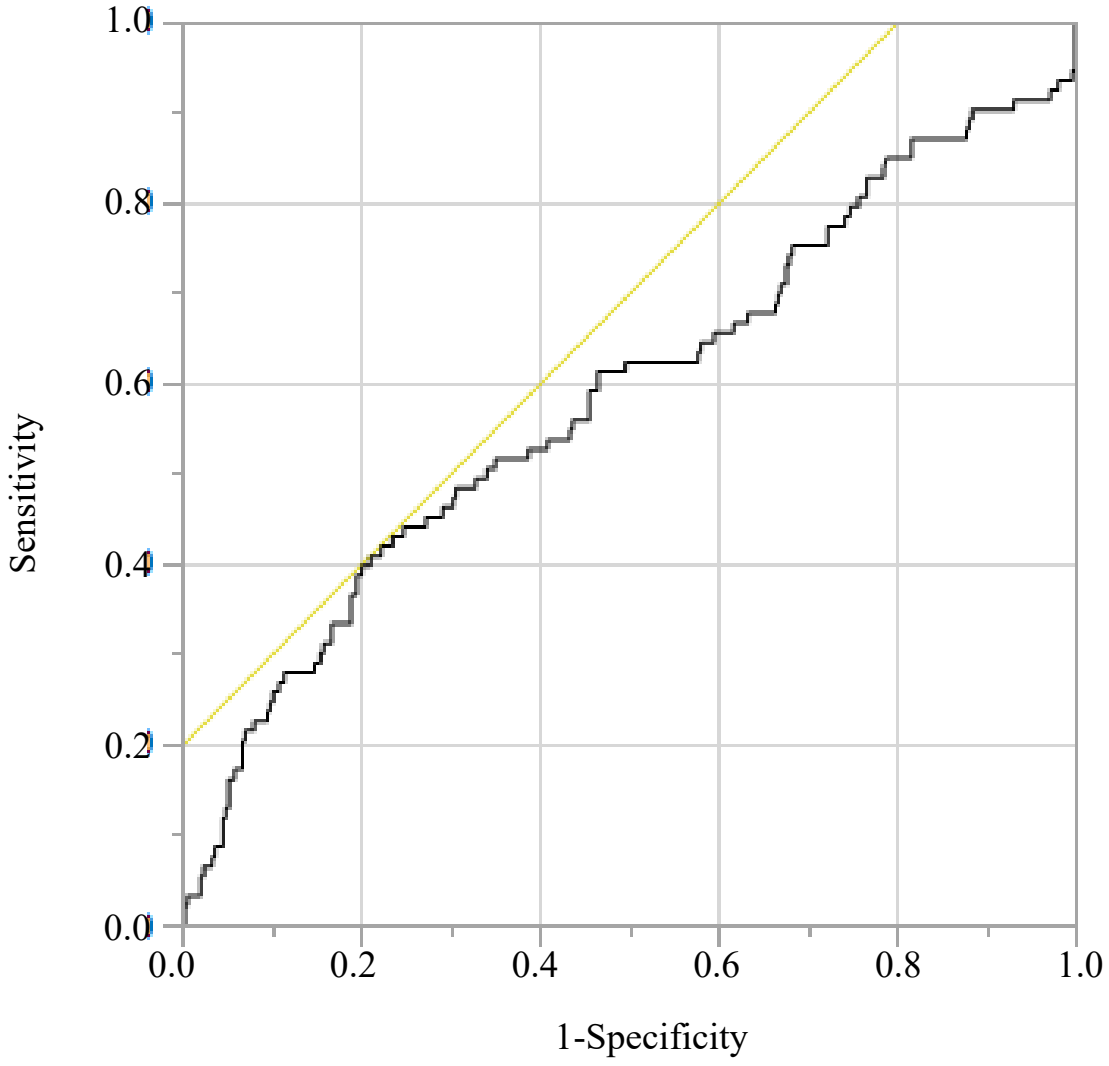

Fig. 1 Receiver operating curve for overall survival was plotted to verify the optimum cutoff value of SII score.

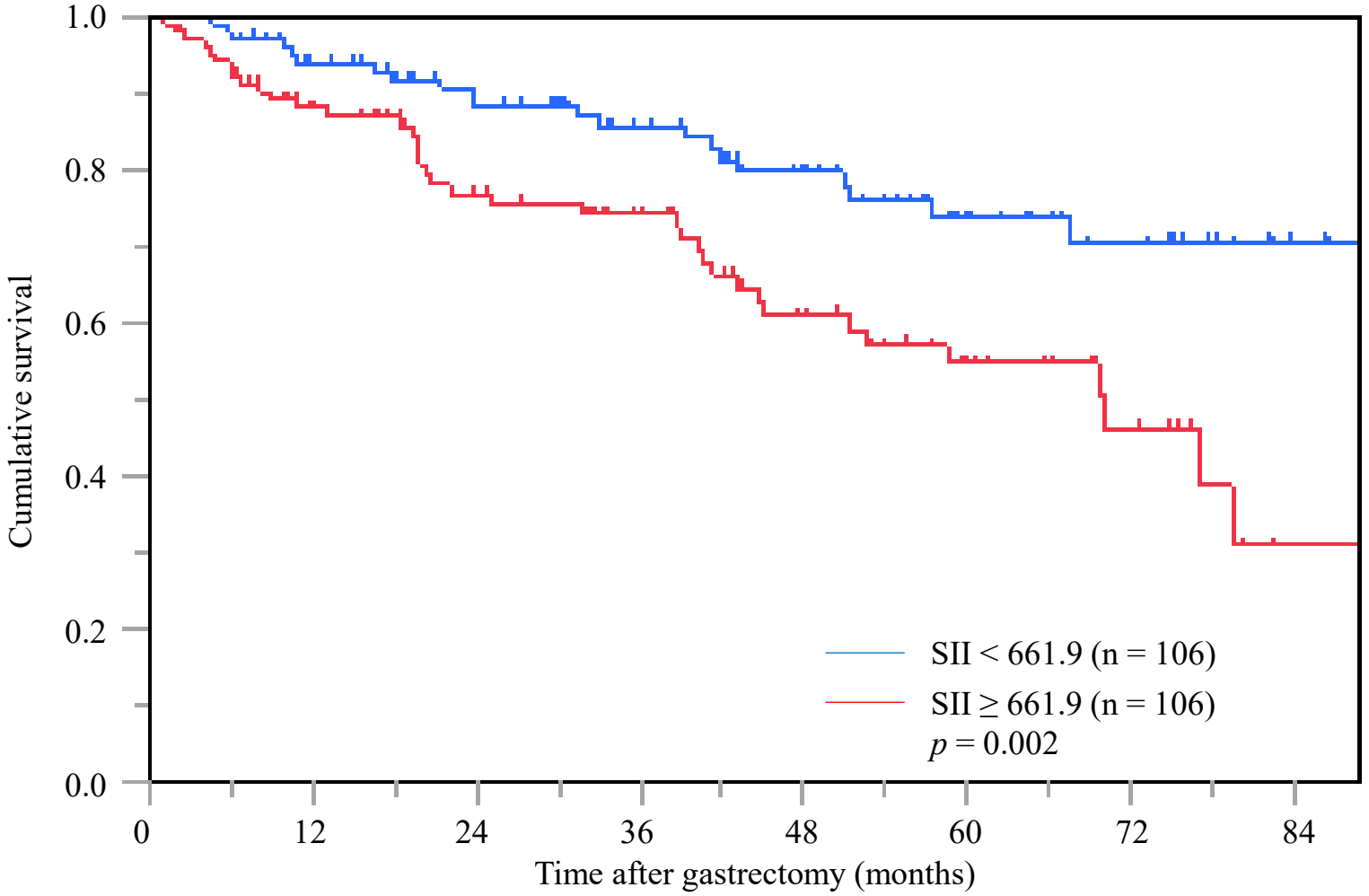

Fig.2 Overall survival based on SII in propensity score matched 212 gastric cancer patients.

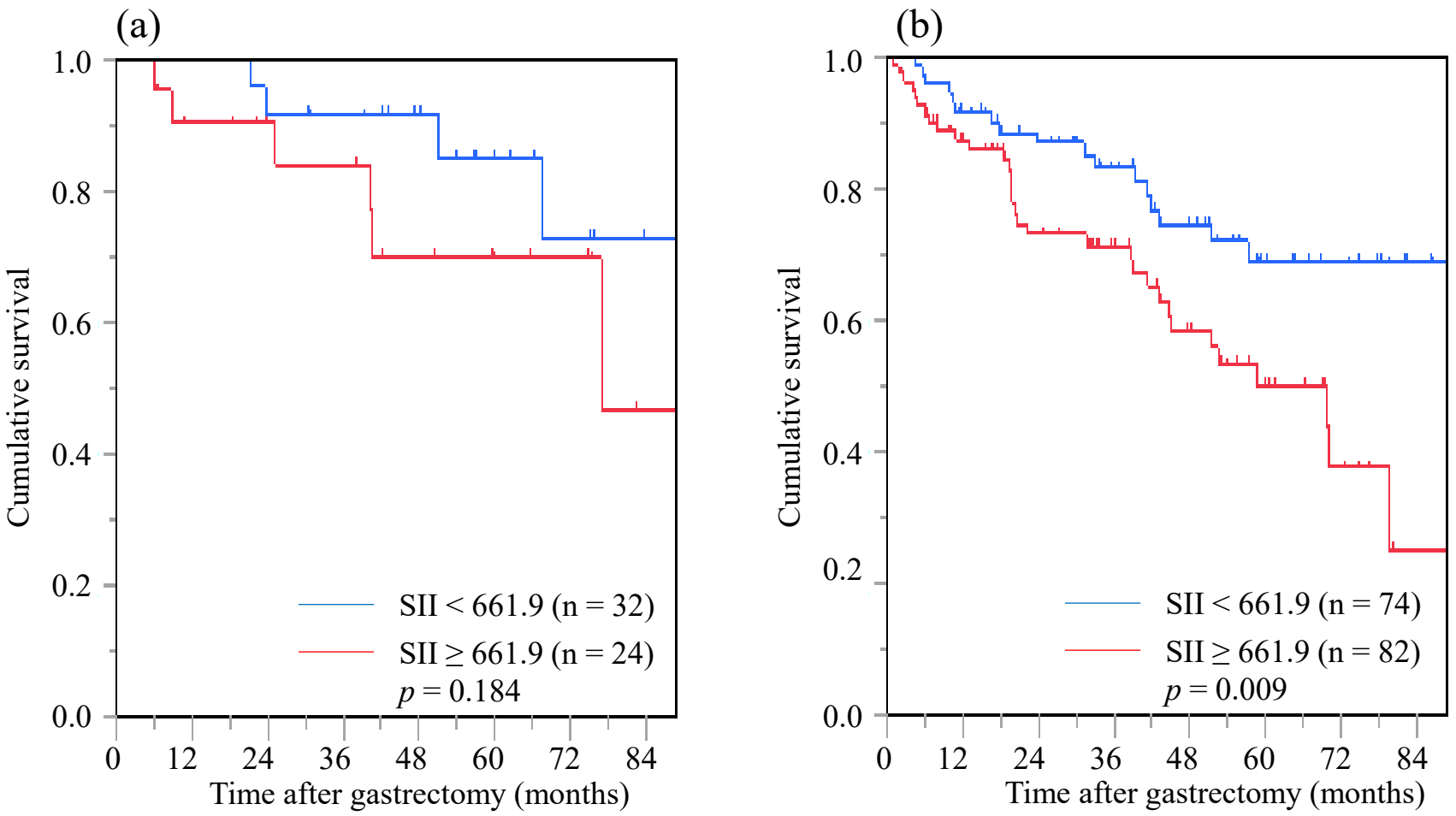

Fig. 3 Postoperative overall survival based on SII in age-stratified gastric cancer patients.
(a) non-elderly patients, (b) elderly patients