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Global Immune-Nutrition-Information Index Is Independent Prognostic Factor for Gastric Cancer Patients Who Received Curative Treatment

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Abstract. *Background/Aim: The aim of the present study was to evaluate the clinical impact of the Global Immune-Nutrition-Information Index (GINI) in patients with gastric cancer (GC) who received curative treatment and to clarify the potential of the GINI as a biomarker. Patients and Methods: Patients who underwent curative resection for GC at Yokohama City University between 2005 and 2020 were selected based on their medical records. The GINI was calculated as follows: GINI=[C-reactive protein × platelet × monocyte × neutrophil]/[albumin × lymphocyte]. Results: A total of 258 patients were included in this study. Of these, 169 patients were categorized into the GINI-low group and 89 into the GINI-high group using a cut-off value of 1,730. The three- and five-year overall survival (OS) rates were 86.4% and 78.4%, respectively, in the GINI-low group, and 66.4% and 58.3% in the GINI-high group (p<0.001). In a multivariate analysis for OS, the GINI was identified as an independent prognostic factor [hazard ratio (HR)=1.772; 95% confidence interval (CI)=1.053-2.979, p=0.031]. Similar results were observed for RFS. In addition, the GINI affected the perioperative clinical course, including postoperative surgical complications and postoperative adjuvant treatment. Conclusion: The GINI is a promising biomarker for the treatment and management of GC.*

Gastric cancer (GC) is the fifth most common cancer and the fourth leading cause of cancer-related death worldwide (1, 2). Perioperative adjuvant treatment and gastrectomy are the standard treatment strategies for locally advanced GC (3, 4). To date, various prognostic factors have been reported and introduced into the treatment and management of GC (5-7). Recently, nutrition and inflammation scores, such as the Glasgow prognostic score (GPS), C-reactive protein to albumin ratio (CAR), Naples prognostic score (NPS), and systemic inflammation score (SIS), have become promising prognostic factors in GC (8-12). Recent studies have demonstrated that nutrition and inflammation scores affect both short- and long-term oncological outcomes (13-16). Therefore, evaluation and improvement of the perioperative nutrition and inflammation status may be useful for GC treatment and management.

The GPS, CAR, NPS, and SIS are calculated using nutritional markers (*e.g.*, albumin or cholesterol) and inflammatory markers (*e.g.*, neutrophils, lymphocytes, monocytes, and platelets). Although albumin, CRP, neutrophils, lymphocytes, monocytes, and platelets are useful for evaluating nutrition and inflammation, there have been no reports on the combined use of all of these elements. Recently, Topkan *et al.* developed and proposed the Global Immune-Nutrition-Information Index (GINI) as a promising biomarker (17). The GINI is calculated using C-reactive protein, platelets, monocytes, neutrophils, albumin, and lymphocytes. This index

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Key Words: GINI, survival, gastric cancer.

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)					0.018
<70	118	97.2	83.7	81.1	
≥70	140	94.1	75.5	62.7	
Sex					0.721
Male	182	97.7	78.7	72.2	
Female	76	90.6	80.2	67.7	
T status					<0.001
T1	140	99.2	96.4	91.6	
T2 to T4	76	90.4	60.6	49.1	
Lymph node metastasis					<0.001
Negative	168	98.1	93.4	84.9	
Positive	90	90.8	54.8	47.6	
GINI					<0.001
≤1,730	169	96.8	86.4	78.4	
>1,730	89	93.2	66.4	58.3	
Lymphatic invasion					<0.001
Negative	146	99.2	92.9	86.1	
Positive	112	90.7	62.2	52.9	
Vascular invasion					<0.001
Negative	152	98.6	90.8	83.3	
Positive	106	91.2	63.7	54.7	
Postoperative surgical complications					0.040
No	163	97.4	83.7	76.3	
Yes	95	92.4	72.6	63.7	

OS: Overall survival; GINI: Global Immune-Nutrition-Inflammation Index.

can evaluate the nutritional and inflammation statuses simultaneously and is highly useful for predicting oncological outcomes. However, no reports have evaluated the clinical impact of the GINI in gastric cancer.

The aim of the present study was to evaluate the clinical impact of GINI for patients with GC who received curative treatment and to clarify the potential of the GINI as a biomarker.

Patients and Methods

Patients. Using medical records, we selected consecutive patients who underwent curative resection for GC at Yokohama City University between 2005 and 2020. The following inclusion criteria were applied: 1) histological diagnosis of adenocarcinoma; 2) clinical stage I-III disease (based on the General Rules of the Japanese Gastric Cancer Association for GC, 15th edition) (18); 3) curative gastrectomy performed as the primary treatment; and 4) the achievement of complete resection of GC (defined as R0) and radical lymph node dissection.

Surgery and adjuvant treatment. In the present study, all patients underwent gastrectomy with either D1+ or D2 nodal dissection. S-1-based adjuvant chemotherapy was administered to patients with pathological stage I or II disease (19, 20).

Calculation of the GINI. The GINI was calculated using the following formula: GINI=[C-reactive protein × Platelets × Monocytes × Neutrophils]/[Albumin × Lymphocytes] (17).

Follow-up. As follow-up evaluations, patients underwent hematological tests, including tumor marker measurements, and physical examinations at least every three months for five years at outpatient clinics. Within the initial three-year postoperative period, they also received computed tomography (CT) examinations every three months. After three years, CT examinations were performed semiannually until five years postoperatively.

Statistical analysis. We used the chi-square test to evaluate the significance of associations between the GINI and clinicopathological factors. Curves for overall and recurrence-free survival were generated using the Kaplan–Meier method. The univariate and multivariate survival analyses were conducted using a Cox proportional hazards model. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SPSS (v27.0 J Win; IBM, Armonk, NY, USA).

Ethical approval. The present study was approved by the review board of Yokohama City University.

Results

Patient background. The study included 258 patients (male, n=140; female, n=118; median age, 70 years). When comparing overall survival (OS) according to the patients' clinicopathological characteristics, the following factors showed statistical significance: age, T status, lymph node

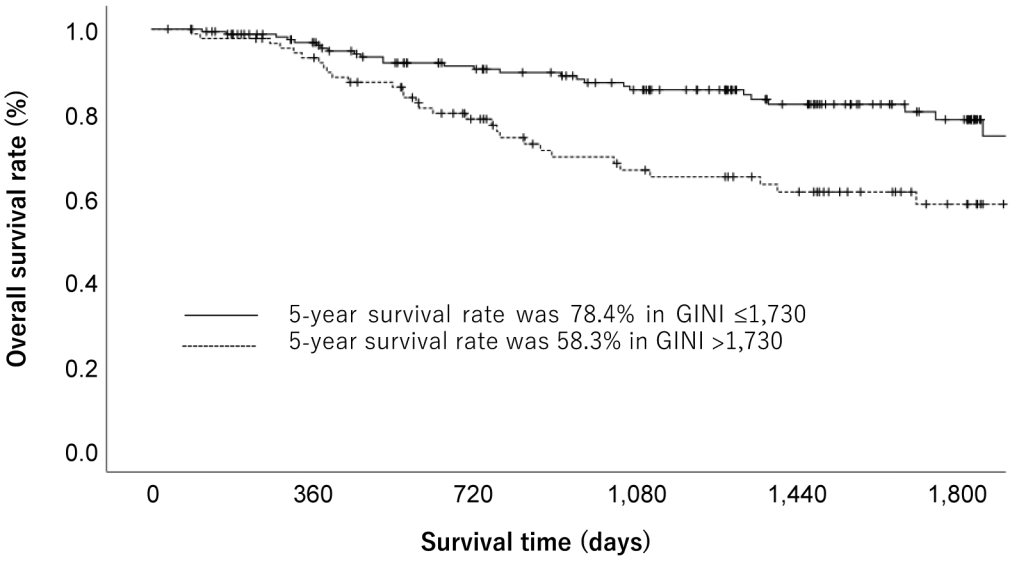

Figure 1. *Overall survival of patients with gastric cancer in the Global Immune-Nutrition-Information Index (GINI)-high and GINI-low groups.*

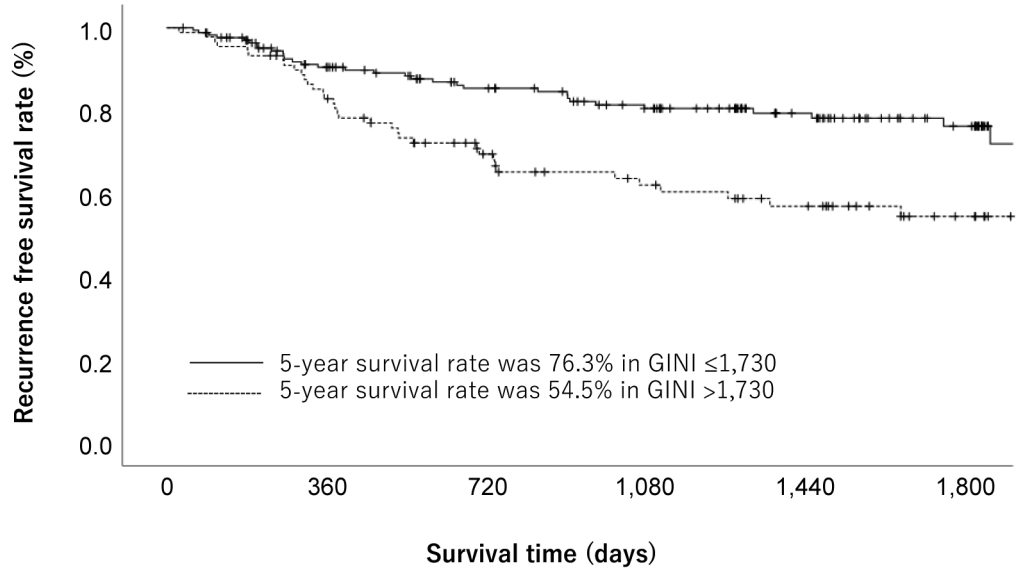

Figure 2. *Recurrence-free survival of patients with gastric cancer in the Global Immune-Nutrition-Information Index (GINI)-high and GINI-low groups.*

metastasis status, lymphovascular invasion status, GINI, postoperative surgical complications, postoperative complications. In the present study, we set the cut-off value of the GINI at 1730 based on previous studies and 3- and 5-year OS (Table I). The patients in the present study were categorized into the GINI-low (n=169) and GINI-high (n=89) groups. The comparison of these groups revealed significant differences in age, lymph node metastasis status, and T status. The GINI-high group included a significantly higher number of elderly patients and patients with an advanced tumor stage.

Survival analysis. The 3- and 5-year OS rates were 86.4% and 78.4%, respectively, in the GINI-low group, and 66.4% and 58.3% in the GINI-high group ($p<0.001$) (Figure 1). The following prognostic factors were identified in the univariate analysis for OS: age, T status, lymphatic invasion, vascular invasion, lymph node metastasis, GINI, and postoperative

Table II. *Uni and Multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.020			0.048
<70	118	1.000			1.000		
≥70	140	1.914	1.107-3.307		1.743	1.006-3.019	
Sex				0.721			
Female	76	1.000					
Male	182	1.105	0.639-1.909				
T status				<0.001			<0.001
T1	140	1.000			1.000		
T2 το T4	118	8.834	4.187-18.638		4.792	2.097-10.952	
Lymph node metastasis				<0.001			0.002
Negative	168	1.000			1.000		
Positive	90	5.908	3.356-10.401		2.661	1.424-4.971	
GINI				<0.001			0.031
≤1,730	169	1.000			1.000		
>1,730	89	2.506	1.497-4.193		1.772	1.053-2.979	
Lymphatic invasion				<0.001			
Negative	146	1.000					
Positive	112	4.570	2.540-8.224				
Vascular invasion				<0.001			
Negative	152	1.000					
Positive	106	4.444	2.500-7.898				
Postoperative complications				0.042			
No	163	1.000					
Yes	95	1.697	1.019-2.829				

GINI: Global Immune-Nutrition-Inflammation Index.

surgical complications (Table II). The GINI was also identified as an independent prognostic factor in the multivariate analysis for OS [hazard ratio (HR)=1.772, 95% confidence interval (CI)=1.053-2.979, p=0.031]. Furthermore, the GINI-low group had three-year and five-year recurrence free survival (RFS) rates of 81.4% and 76.3% respectively. In contrast, the GINI-high group had three-year and five-year RFS rates of 63.7% and 54.5%, respectively (p<0.001) (Figure 2). The univariate analysis for RFS identified the following prognostic factors: T status, lymph node metastasis, lymphatic invasion, vascular invasion, GINI, and postoperative surgical complications (Table III). In the multivariate analysis for RFS, the GINI was identified as a marginally significant prognostic factor (HR=1.813, 95%CI=0.969-3.394, p=0.063).

Comparison of postoperative clinical course. When the sites of recurrence were compared between the two groups, the GINI-high group had a significantly higher peritoneal recurrence rate than the GINI-low group (21.3% *vs*. 7.1%, p<0.001) (Table IV). When the postoperative surgical complications were compared in detail, there was a significantly higher incidence of abdominal abscess in the GINI-high group (5.6% *vs*. 1.2%, p=0.037).

In the clinical course, 31.4% of patients in the GINI-low group and 56.2% of the patients in the GINI-high group required postoperative adjuvant chemotherapy (p<0.001). However, the postoperative adjuvant chemotherapy rates in the GINI-low and GINI-high groups were 64.1% and 52.0%, respectively. Although the difference did not reach statistical significance patients in the GINI-low group tended to be introduced to adjuvant chemotherapy more frequently (p=0.211).

Discussion

The aim of the present study was to clarify the clinical impact of GINI in patients with GC who received curative treatment. In the present study, we first demonstrated that the GINI is an independent prognostic factor for patients with GC. In addition, the GINI affects the perioperative clinical course, such as postoperative surgical complications and postoperative adjuvant treatment. Therefore, the GINI could be a promising biomarker for GC treatment and management.

In the present study, the GINI was found to be an independent prognostic factor. The HR was 1.772 (95%CI=1.053-2.979, p=0.031). Similar results have been reported in previous studies.

Table III. *Uni and Multivariate Cox proportional hazards analysis 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)				0.127			
<70	118	1.000					
≥70	140	1.459	0.898-2.372				
Sex				0.691			
Female	76	1.000					
Male	182	1.111	0.661-1.867				
T status				<0.001			0.010
T1	140	1.000			1.000		
T2 to T4	118	7.893	4.141-15.046		2.812	1.286-6.145	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	6.652	3.949-11.203		2.944	1.631-5.312	
GINI				<0.001			0.063
≤1,730	169	1.000			1.000		
>1,730	89	2.335	1.457-3.740		1.813	0.969-3.394	
Lymphatic invasion				<0.001			
Negative	146	1.000					
Positive	112	4.332	2.555-7.347				
Vascular invasion				<0.001			
Negative	152	1.000					
Positive	106	5.152	3.010-8.817				
Postoperative complications				0.014			0.047
No	163	1.000			1.000		
Yes	95	1.805	1.129-2.885		1.623	1.006-2.620	

GINI: Global Immune-Nutrition-Inflammation Index.

Topkan *et al*. investigated the prognostic impact of the GINI in 802 patients with stage IIIC non-small lung cancer (NSCLC) who received chemoradiation therapy (17). The patients were divided into a GINI-low group (n=364) and a GINI-high group (n=438) using a cut-off value of 1562. There were significant differences in the median OS and 5-years OS between the two groups. The median OS was 37.8 months in the GINI-low group, while 19.1 months in the GINI-high group ($p<0.001$). Moreover, the 5-years OS was 32.1% in the GINI-low group and 7.9% in the GINI-high group ($p<0.001$). In the multivariate analysis, the GINI was an independent prognostic factor for OS ($p<0.001$).

There are two possible explanations as to why the GINI affects the patients with GC. The first is that the GINI affects postoperative surgical complications. In the present study, the incidence of abdominal abscess was significantly higher in the GINI-high group than in the GINI-low group (5.6% *vs*. 1.2%, $p=0.037$). Recent studies demonstrated that postoperative surgical complications affected patient survival in various malignancies (21, 22). Thus, the GINI status affects postoperative surgical complications, resulting in poor prognosis. The second possibility is that the GINI affects the clinical course of chemotherapy. In the present study, patients diagnosed with pathological stage II or III after surgery received postoperative adjuvant chemotherapy. In the present study, postoperative adjuvant chemotherapy needed 31.4% of the patients in the GINI-low group and 56.2% in the GINI-high group. A significant difference was observed between the groups ($p<0.001$). In contrast, the percentage of patients who received postoperative adjuvant chemotherapy was 64.1% and 52.0% of patients in the GINI-low and GINI-high groups, respectively. The incidence of patients who received adjuvant chemotherapy

Table IV. *Patterns of recurrence according to Global Immune-Nutrition-Inflammation Index (GINI).*

	GINI				*p*-Value
	≤1,730 (n=169)		>1,730 (n=89)		
Recurrence site	Number	%	Number	%	
Peritoneal recurrence	12	7.1	19	21.3	<0.001
Lymph node recurrence	8	4.7	9	10.1	0.098
Hematological recurrence	12	7.1	13	14.6	0.053

was higher in the GINI-low group than in the GINI-high group. These results suggest that patients in the GINI-high group required adjuvant chemotherapy therapy, but fewer actually received adjuvant chemotherapy, suggesting that patients in the GINI-high group may not have benefited from adjuvant therapy. Similar results were observed by Topkan (17). They reported that the introduction of maintenance chemotherapy was significantly lower in the GINI-high group than in the GINI-low group (33.8% *vs.* 24.0%, p=0.029). In addition, the GINI status also affected the adverse effects of chemotherapy. Topkan *et al*. found a relationship between the GINI status and the clinical course of chemotherapy. They demonstrated that the GINI status affects adverse events due to chemoradiation therapy. Acute grade 3-4 toxicity and late grade 3-4 toxicity were significantly higher in the GINI-high group than in the GINI-low group (42.2% *vs.* 25.0%, p=0.009) (10.3% *vs.* 4.9%, p=0.037, respectively). Considering these factors, the GINI status affects the clinical course of chemotherapy, including adjuvant treatment, resulting in a poor prognosis.

Study limitations. First, this was a retrospective study conducted at a single institution. Therefore, there is an inherent selection bias. Second, there may have been time bias. This study included patients who were treated between 2005 and 2020. During this period, the standard perioperative adjuvant treatment for GC changed. Third, the optimal cut-off value for the GINI remains unclear. To utilize the GINI in the clinical setting for the treatment and management of GC, it is necessary to set an optimal cutoff value. We set the cutoff value of the GINI at 1,730 according to the 3- and 5-year survival rates. In contrast, Topkan *et al*. set the cutoff value of the GINI at 1562. These differences might be due to differences in patient background factors, number of patients, treatment methods, or the methods used to determine the cut-off value of the GINI. Thus, further studies are needed to determine the optimal cut-off value for the GINI. Considering these findings, our study should be validated in a larger cohort.

In conclusion, the GINI is an independent prognostic factor for GC. In addition, the GINI status also affected postoperative surgical complications and the clinical course of postoperative adjuvant chemotherapy. Thus, the GINI may be a promising biomarker for GC treatment and management.

Conflicts of Interest

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

Authors' Contributions

TA and IH contributed substantially to this concept and study design. TA, IH, YM, MN, AY, SY, RE, MT, JM, NY, AS, YR, TO, MN, and HC made substantial contributions to the data acquisition, analysis, and interpretation. TA, MN, AS, TA, KS, TO, NY, and YR were involved in drafting and critically revising the manuscript for important intellectual content. TA and YM approved the final version of the manuscript.

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