

# Albumin-Globulin Ratio Is an Independent Prognostic Factor for Gastric Cancer Patients who Received Curative Treatment

MOMOKO FUKUDA<sup>1\*</sup>, TORU AOYAMA<sup>1,2\*</sup>, ITARU HASHIMOTO<sup>1</sup>, YUKIO MAEZAWA<sup>1,2</sup>,  
AYA KATO<sup>1</sup>, KENTARO HARA<sup>1,3</sup>, KEISUKE KAZAMA<sup>1</sup>, KEISUKE KOMORI<sup>1</sup>, AYAKO TAMAGAWA<sup>1</sup>,  
HARUHIKO CHO<sup>1,2</sup>, TETSUSHI ISHIGURO<sup>1</sup>, KENKI SEGAMI<sup>1</sup>, MASATO NAKAZONO<sup>1</sup>,  
KAZUKI OTANI<sup>1</sup>, SHO SAWAZAKI<sup>1</sup>, MASAKATSU NUMATA<sup>1</sup>, SHINNOSUKE KAWAHARA<sup>1</sup>,  
TAKASHI OSHIMA<sup>1,3</sup>, AYA SAITO<sup>1</sup>, NORIO YUKAWA<sup>1</sup> and YASUSHI RINO<sup>1</sup>

<sup>1</sup>Department of Surgery, Yokohama City University, Yokohama, Japan;

<sup>2</sup>Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan;

<sup>3</sup>Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

**Abstract.** *Background/Aim:* The albumin-globulin ratio (AGR) is a useful biomarker for predicting postoperative complications and a poor prognosis in patients with various types of cancer and can be evaluated without invasive testing or surgery. In this study, we aimed to evaluate the usefulness of the AGR in predicting the short- and long-term prognoses of patients with gastric cancer who underwent radical resection at our institution. *Patients and Methods:* This study is a retrospective cohort analysis in which eligible patients were selected from the medical records of patients who underwent radical resection for gastric cancer at Yokohama City University from 2000 to 2020 and their medical records were reviewed. A total of 240 patients with gastric cancer were classified into high-AGR (>1.57) and low-AGR ( $\leq 1.57$ ) groups and their overall survival (OS), recurrence-free survival (RFS), and postoperative complication rates were compared. *Results:* Of the total 240 patients, 87 were classified into the high AGR group and 153 were classified into the low AGR group; the incidence of postoperative

complications in the two groups did not differ to a statistically significant extent (34.4% vs. 39.2%,  $p=0.491$ ). The long-term findings showed that the 5-year OS and RFS rates were significantly better in the high AGR group [84.0% vs. 64.8% ( $p=0.005$ ), 80.0% vs. 61.9% ( $p=0.015$ ), respectively]. *Conclusion:* Preoperative low AGR is a risk factor for OS and DFS in patients with gastric cancer who undergo surgery. The AGR may be a useful biomarker that can be applied as a prognostic indicator for patients with gastric cancer.

Gastric cancer is associated with high morbidity and mortality, which is responsible for more than 1 million new cases and 769,000 deaths annually worldwide (1, 2). Local resection and systemic chemotherapy (postoperative chemoradiotherapy in the United States, perioperative chemoradiotherapy in Europe, and postoperative chemotherapy in Asia) are commonly used as standard treatments for gastric cancer that has not spread to other organs (3-5). However, postoperative recurrence of gastric cancer is not uncommon, and the prognosis after recurrence is poor (6, 7). Therefore, it is important to evaluate the risk of recurrence and prognosis of patients with gastric cancer in order to make appropriate treatment choices for each patient and to accurately predict their prognosis.

Recently, many prognostic factors for cancer have been reported, among which the albumin-globulin ratio (AGR) may be a useful biomarker for predicting postoperative complications and a poor prognosis in patients with various types of cancer (8-10). The AGR, the ratio of albumin (an indicator of the nutritional status and the production of which is reduced by inflammatory cytokines) to globulin (which is elevated by increased acute phase proteins and may be associated with apoptosis and cancer progression) is an item that can be obtained from routine blood collection and evaluated without invasive testing or surgery. The prognostic

\*These Authors equally contributed to this study.

*Correspondence to:* Toru Aoyama, Department of Surgery, Yokohama City University, Yokohama, Japan. Tel: +81 457872800, e-mail: t-aoyama@lilac.plala.or.jp; Itaru Hashimoto, Department of Surgery, Yokohama City University, Yokohama, Japan. Tel: +81 457872800, e-mail: itarum1n1@hotmail.com

**Key Words:** Gastric cancer, AGR, albumin, globulin.



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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)					0.008
<75	170	97.4	82.8	78.4	
≥75	70	95.6	70.2	57.7	
Sex					0.477
Male	173	98.2	77.7	71.5	
Female	67	93.7	82.7	73.2	
T status					<0.001
T1	127	99.1	96.0	91.2	
T2 to T3	113	94.4	61.5	52.9	
Lymph node metastasis					<0.001
Negative	154	98.6	94.2	86.6	
Positive	86	95.2	55.1	49.4	
Albumin-Globulin ratio					0.003
>1.57	87	97.5	88.0	84.0	
≤1.57	153	96.5	73.6	64.8	
Lymphatic invasion					<0.001
Negative	136	99.2	93.2	86.3	
Positive	104	94.0	61.3	54.9	
Vascular invasion					<0.001
Negative	141	98.5	91.0	85.3	
Positive	99	95.8	63.0	54.9	
Postoperative surgical complications					0.023
No	150	98.5	84.1	78.8	
Yes	90	94.2	72.4	63.5	
Histological type					0.078
Intestinal	129	98.2	85.6	76.9	
Diffuse	111	95.4	72.4	67.5	

OS: Overall survival.

value of the AGR for patients with gastric cancer has been increasingly reported in many countries (11, 12).

Therefore, we aimed to investigate the usefulness of AGR for predicting the short-term and long-term prognoses of patients with gastric cancer who underwent radical resection at our institution.

## Patients and Methods

**Patients.** Patients eligible for inclusion in the study were identified from the medical records of individuals who had undergone surgical radical resection for gastric cancer at Yokohama City University between the years 2000 and 2020. The inclusion criteria were as follows: 1) histologically confirmed gastric cancer, 2) clinical stage I-III according to the 8th edition of the Tumor-Node-Metastasis classification (published by the Union for International Cancer Control), and 3) complete resection of gastric cancer, defined as R0, in addition to radical lymph node dissection (13). Patients who did not meet these criteria, including those who received R1 or R2 resection, were excluded.

**Surgery and adjuvant treatment.** In all cases, laparoscopic or open, robot-assisted resection of ≥2/3 of the stomach and total gastrectomy, plus lymph node dissection was performed. Patients with clinical Stage IA disease received D1+ lymph node dissection, and patients

with clinical Stage ≥IB disease received D2 lymph node dissection. Patients with pathological stage II/III disease underwent 1 year of postoperative adjuvant chemotherapy. Generally, S-1 monotherapy was administered to patients with pathological stage II disease, while S-1 with docetaxel or capecitabine plus oxaliplatin was administered to patients with pathological stage III disease.

**Postoperative complications.** In the present study, postoperative complications were defined as Clavien-Dindo (version 2.0) Grade ≥II complications, according to the definitions of the Japan Clinical Oncology Group (14).

**Follow-up.** All patients underwent postoperative follow-up examinations at 3-6 months, during which information on survival, disease progression, and time of death was documented for a minimum of 5 years where feasible. The patients' serum tumor marker levels, including carcinoembryonic antigen and carbohydrate antigen 19-9, were assessed at intervals of at least 3-6 months, and computed tomography scans were conducted at least every 6-12 months.

**Evaluation of the pathological response.** The pathologic response to postoperative chemotherapy was characterized in accordance with international criteria, specifically the Response Evaluation Criteria in Solid Tumors (RECIST), as follows: 1) Complete response (CR), defined as complete tumor elimination; 2) Partial response (PR) defined as a ≥30% reduction in the sum of tumor sizes; 3) Stable

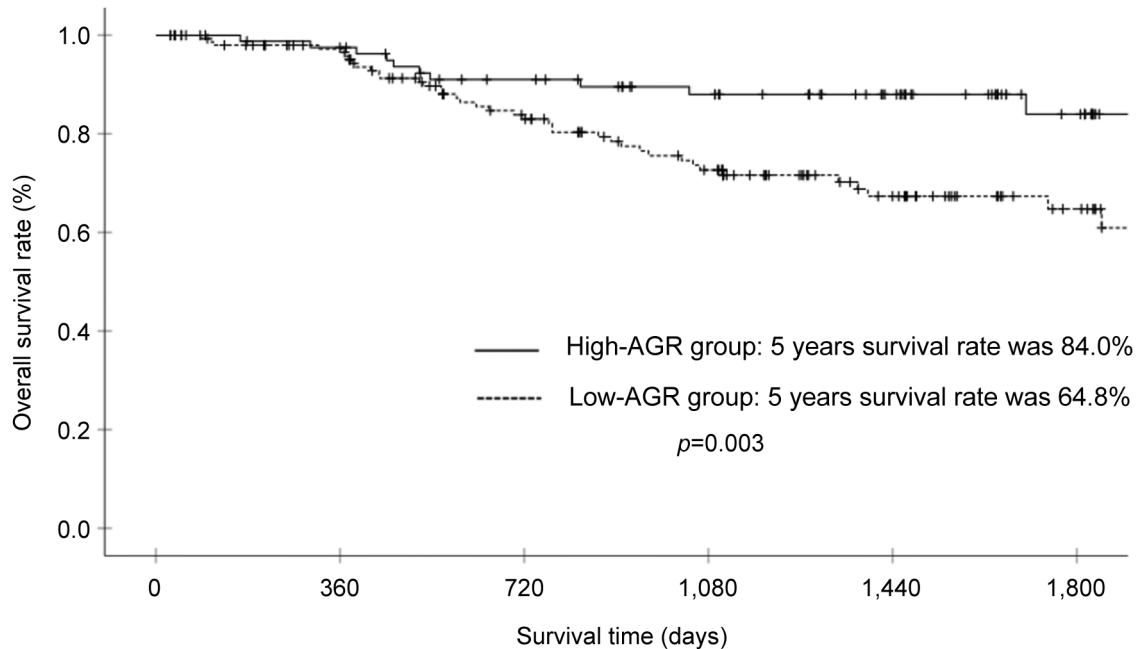


Figure 1. Overall survival of patients with gastric cancer in the high albumin-globulin ratio (AGR) group ( $>1.57$ ) and low AGR group ( $\leq 1.57$ ).

disease (SD), defined as no change in tumor size, and 4) Progressive disease (PD) defined as a  $\geq 20\%$  increase in the sum of tumor sizes along with an absolute increase of  $\geq 5$  mm, or the emergence of a new lesion (15).

**Determination of the albumin-globulin ratio.** The AGR was determined by assessing a preoperative blood sample and dividing the serum albumin level by the serum globulin level, which is calculated as the difference between the serum total protein level and the serum albumin level.

**Statistical analyses.** Categorical variables are expressed as frequencies and percentages (%). Comparative analyses between groups were carried out utilizing the Chi-square test, Student's *t*-test, and Mann-Whitney test. The Kaplan-Meier method was employed for the generation of overall survival (OS) and recurrence-free survival (RFS) curves. A log-rank test was used to compare the equality of survival curves. Univariate and multivariate hazard ratios were computed using the Cox proportional hazards model. All variables identified as significant in the univariate analysis were incorporated into the backward stepwise multivariate model. *p*-Values of  $<0.05$  were considered to indicate statistical significance. All of the statistical analyses were conducted using SPSS (version 27.0, SPSS, Chicago, IL, USA).

## Results

**Patient background.** A total of 240 patients with gastric cancer were selected for this study (Table I). Among the 240 patients, 173 were male and 67 were female. The surgical treatments included total gastrectomy ( $n=56$ ), distal resection ( $n=166$ ),

proximal resection ( $n=5$ ), and partial resection ( $n=1$ ). D1 and D1+, D2, D3, sentinel lymph node dissection was performed in three, 114, 105, one, and one patient, respectively. Based on the patients' 1-, 3-, and 5-year OS rates, and using a cutoff value of 1.57, 87 out of the 240 patients were classified into the high AGR ( $>1.57$ ) patient group, while 153 were classified into the low AGR ( $\leq 1.57$ ) patient group. When each clinicopathological factor was examined, patients in the low AGR group were significantly more likely to be older, have a high ASA-PS, a history of Chronic Obstructive Pulmonary Disease (COPD), a high T factor, venous infiltration, anticoagulant treatment, and drink alcohol.

**Survival analysis and recurrence pattern.** The 5-year postoperative overall survival (OS) rate was 84.0% in the high AGR group and 64.8% in the low AGR group ( $p=0.003$ ). The OS curves are shown in Figure 1. Each clinicopathological factor was analyzed as presented in Table I. OS was compared between groups using log-rank testing. There were significant differences in age ( $<75$  vs.  $\geq 75$ ), UICC T status (T1 vs. T2-T3), lymph node metastasis, AGR ( $\leq 1.57$  vs.  $>1.57$ ), lymphatic invasion, vascular invasion, and postoperative surgical complications. The univariate analysis (Table II) of overall survival showed that age, T status, lymph node metastasis, AGR, lymphatic invasion, vascular invasion, and postoperative surgical complications were significantly associated with OS. In the multivariate analysis (Table II), AGR emerged as an independent predictor of OS

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)				0.010			
<75	170	1.000					
≥75	70	2.080	1.193-3.627				
Sex				0.478			
Male	173	1.000					
Female	67	1.264	0.661-2.415				
T status				<0.001			0.006
T1	127	1.000			1.000		
T2 or T3	113	8.085	3.639-17.960		3.508	1.427-8.625	
Lymph node metastasis				<0.001			<0.001
Negative	154	1.000			1.000		
Positive	86	6.324	3.363-11.893		3.455	1.707-6.990	
Albumin-Globulin ratio				0.005			0.040
>1.57	87	1.000			1.000		
≤1.57	153	2.709	1.356-5.414		2.104	1.034-4.280	
Lymphatic invasion				<0.001			
Negative	136	1.000					
Positive	104	4.462	2.371-8.399				
Vascular invasion				<0.001			
Negative	141	1.000					
Positive	99	4.708	2.504-8.850				
Histological type				0.081			0.041
Intestinal	129	1.000			1.000		
Diffuse	111	1.643	0.940-2.870		1.801	1.023-3.170	
Postoperative complications				0.025			
No	150	1.000					
Yes	90	1.880	1.082-3.265				

[odds ratio (OR)=2.104, 95% confidence interval (CI)=1.034-4.280,  $p=0.040$ ]. The 5-year postoperative RFS rate was 80.0% in the high AGR group and 61.9% in the low AGR group ( $p=0.010$ ). The RFS curves are shown in Figure 2. The univariate analysis of RFS demonstrated that the AGR was a significant prognostic factor (Table III). A comparison of recurrence patterns between the high and low AGR groups revealed a significant difference in hematological recurrence (3.4% vs. 14.3%,  $p=0.008$ ) (Table IV).

**Postoperative clinical course.** A subgroup analysis was performed for the AGR, and clinicopathological factors, such as sex, age, medical history (diabetes, hypertension, COPD), ASA-PS, surgical technique, lymph node dissection area, vascular invasion, T factor, N factor, presence of blood transfusion, postoperative complications, anticoagulation medication, alcohol consumption, and smoking were examined. Postoperative complications were compared overall and for pancreatic fistula, anastomotic stenosis, intra-abdominal abscess, and suture failure. No significant differences were observed.

## Discussion

The AGR is a potential prognostic factor in various types of cancer and has been increasingly reported in recent years. This study was conducted to investigate the usefulness of a low preoperative AGR as a prognostic factor in postoperative gastric cancer patients. The results showed that the preoperative AGR is a risk factor for OS and DFS after the surgical treatment of gastric cancer. Furthermore, patients with a low AGR who underwent surgery for gastric cancer had a worse prognosis than those with a high AGR. Therefore, the AGR will be applicable as a prognostic indicator in patients with gastric cancer in the future.

In the present study, we demonstrated that the AGR was one of the promising prognostic factors. Similar results have been reported in previous studies on the AGR; in a meta-analysis of 12 cohorts, Wei *et al.* compared 8305 patients with gastric cancer with low pretreatment AGRs to those with high AGRs (16). The cutoff values ranged from 1.14 to 1.93, and they found that OS (HR=1.531, 95%CI=1.300-1.803,  $p<0.001$ ) and DFS/PFS (HR=2.008, 95%CI=1.162-3.470,  $p=0.012$ ) were

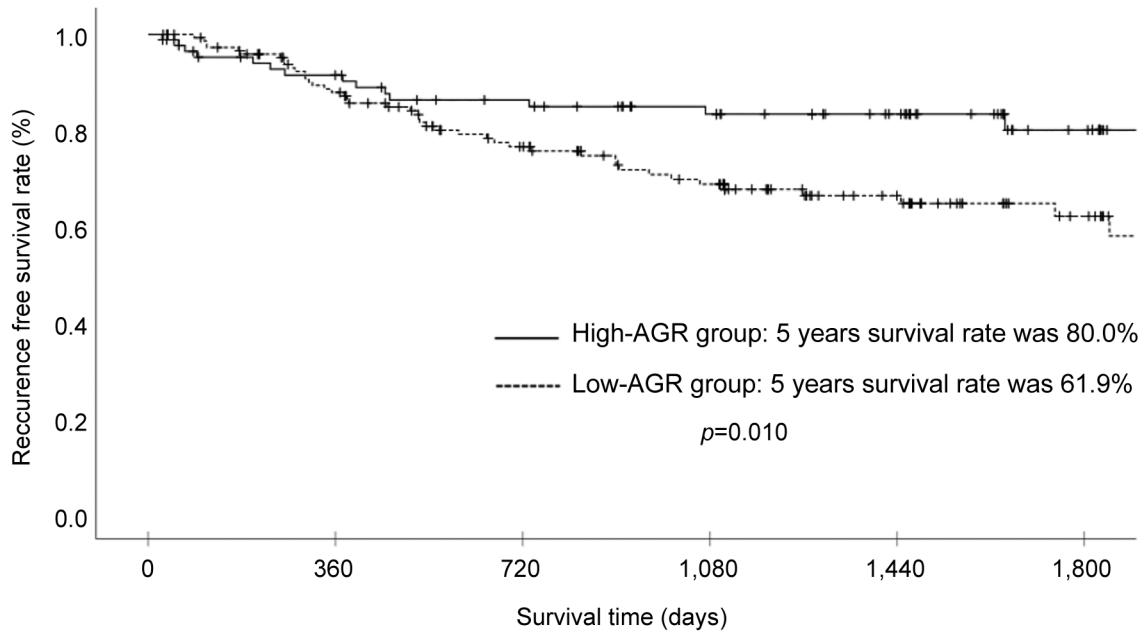


Figure 2. Recurrence-free survival of patients with gastric cancer in the high albumin-globulin ratio (AGR) group (>1.57) and low AGR group ( $\leq 1.57$ ).

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)				0.031			
<75	170	1.000					
$\geq 75$	70	1.769	1.054-2.969				
Sex				0.311			
Male	173	1.000					
Female	67	1.345	0.739-2.449				
T status				<0.001			0.038
T1	127	1.000			1.000		
T2 or T3	113	7.018	3.555-13.852		2.357	1.049-5.295	
Lymph node metastasis				<0.001			<0.001
Negative	154	1.000			1.000		
Positive	86	7.363	4.093-13.244		3.501	1.789-6.851	
Albumin-Globulin ratio				0.015			
>1.57	87	1.000					
$\leq 1.57$	153	2.109	1.158-3.841				
Lymphatic invasion				<0.001			
Negative	136	1.000					
Positive	104	3.991	2.271-7.014				
Vascular invasion				<0.001			0.044
Negative	141	1.000			1.000		
Positive	99	4.922	2.772-8.739		2.022	1.019-4.009	
Histological type				0.239			0.092
Intestinal	129	1.000			1.000		
Diffuse	111	1.357	0.816-2.257		1.563	0.930-2.627	
Postoperative complications				0.014			0.045
No	150	1.000			1.000		
Yes	90	1.889	1.137-3.137		1.690	1.013-2.819	

Table IV. Patterns of recurrence according to albumin-globulin ratio.

Recurrence site	Albumin-Globulin ratio				p-Value
	>1.57 (n=87)		≤1.57 (n=153)		
	Number	%	Number	%	
Peritoneal recurrence	7	8.0	20	13.0	0.236
Hematological recurrence	3	3.4	22	14.4	0.008
Lymph node recurrence	6	6.9	8	5.2	0.596
Local site	2	2.3	9	5.9	0.202

obviously shorter in GC patients with low pretreatment AGRs than in those with elevated AGRs, which indicated that a low pretreatment AGR could predict a poor prognosis in patients with GC. Among them, Toiyama *et al.* showed that in 384 patients with gastric cancer, the cutoff value of the preoperative AGR (determined using ROC curves) was 1.3793, indicating that the low preoperative AGR group had poorer DFS than the high AGR group. (HR=1.7264, 95%CI=1.0032-2.9709,  $p=0.0498$ ) (17). Furthermore, a low AGR was associated with advanced cancer and early postoperative recurrence, indicating that it may be an independent predictor of recurrence in patients after radical gastric cancer surgery.

Although the mechanism underlying the association between the AGR and patient survival is unclear, there are some possible explanations. First, the AGR status might have some clinical impact on lymph node metastasis. For example, Jieshan *et al.*, who analyzed 14 studies involving 4136 patients with various carcinomas revealed that cancer patients in the low AGR group exhibited a heightened risk of lymph node metastasis (HR=2.24, 95%CI=1.49-3.36,  $p<0.001$ ) (18). In this study, the rate of lymph node metastasis in the high and low AGR groups did not differ to a statistically significant extent, but the T factor was more advanced in the low AGR group in comparison to the high AGR group. Thus, it can be inferred that gastric cancer was detected at a more advanced stage in the low AGR group, which would be related to the determinants of stage. Second, the AGR status might have some clinical impact on synchronous and/or metachronous other primary cancer occurrence. For example, Suh *et al.* investigated 26,974 healthy adults grouped by AGR values and found that those with a lower AGR were at a higher risk of developing various cancers, including liver and blood cancers (19). In the present study, complications of diabetes, hypertension, and COPD were compared in the high AGR and low AGR groups, but other primary cancers were not examined. Among the complications studied, the incidence of COPD was higher in the low AGR group.

*Study limitations.* First, it was a retrospective study that was conducted in a single center, which evaluated a single group

of cases. Second, serum proteins, such as albumin and globulin may be affected by unknown substances. Third, the optimal cutoff value of AGR is unclear. Although there is no clear definition for the cutoff value of AGR, previous reports have used values of 1.14 to 1.93, and an AGR of 1.57 was used as the cutoff value in this study, which is similar to the values reported in other studies. Considering these limitations, a large, multicenter, prospective study is needed to conduct a precise evaluation.

In conclusion, this study suggested that a low preoperative AGR is a risk factor for OS and DFS in postoperative patients with gastric cancer; the AGR may be a useful biomarker that can be applied as a prognostic indicator for gastric cancer patients.

### Conflicts of Interest

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

### Authors' Contributions

MF, AK, and YM made substantial contributions to the concept and design. TA, KH, KK1(Keisuke Kazama), KK2 (Keisuke Komori), HT, AT, IH, OK, NK, and HC made substantial contributions to the acquisition of data and the analysis and interpretation of the data. TA, JM, KS, MI, TO, AS, NY, and YR were involved in drafting the article or revising it critically for important intellectual content. TA and YM gave their final approval of the version to be published.

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