

C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer

MINJIE MAO^{1*}, XIAOLI WEI^{2*}, HUI SHENG^{3*}, PEIDONG CHI¹, YIJUN LIU¹, XIAOYAN HUANG⁴, YIFAN XIANG⁴, QIANYING ZHU¹, SHAN XING¹ and WANLI LIU¹

Departments of ¹Clinical Laboratory, ²Medical Oncology and ³Experimental Research, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong 510060; ⁴Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong 510275, P.R. China

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Abstract. Multiple studies have reported the prognostic association of certain inflammatory factors with various types of cancer. The present study assessed the prognostic value of the C-reactive protein (CRP)/albumin (Alb) ratio and the neutrophil/lymphocyte ratio (NLR), separately and in combination, in gastric cancer (GC). A total of 337 cases pathologically diagnosed with gastric adenocarcinoma were retrospectively evaluated. The clinicopathological and prognostic relevance of the CRP/Alb ratio and NLR and their combination were analyzed. The optimal cut-off values of the CRP/Alb ratio and NLR were 0.38 and 3.14, respectively. High CRP/Alb ratio (≥ 0.38) and NLR (≥ 3.14) values were associated with increased tumor invasion, more distant metastasis and a more advanced tumor-node-metastasis stage (all $P < 0.05$). In addition, a high NLR value was also associated with increased tumor size ($P = 0.02$). The CRP/Alb ratio ($\geq 0.38 / < 0.38$) and NLR ($\geq 3.14 / < 3.14$) were independent prognostic factors for overall survival time (OS) in GC by multivariate analysis ($P = 0.005$ and $P = 0.001$). Using the CRP/Alb ratio and NLR classification, patients were stratified into three subgroups

with different OS time ($P < 0.001$), which were identified as independent prognostic variables in multivariate analysis ($P < 0.001$). The present study demonstrated that the CRP/Alb ratio and NLR were independent prognostic factors for OS in patients with GC. The combination of these indexes was associated with significant prognostic value and may further stratify prognosis.

Introduction

Gastric cancer (GC) is one of the most common types of tumor globally. In 2015, GC had the second highest incidence and rate of mortality among cancer patients in China (1). Due to the rapid progression of GC and the absence of early specific symptoms and signs, the majority of patients are diagnosed at the late stage of gastric carcinoma (2-5). At present, surgery is the preferred treatment for patients without distant metastasis, and postoperative metastasis and recurrence are the predominant causes of mortality (3,5). Although disease-free and overall survival (OS) may be improved by postoperative chemotherapy and radiotherapy, the prognosis of GC remains poor (3,6). Identifying simple but effective prognostic markers for GC remains an important aim for researchers.

Inflammation occurs in various types of tumor, and serves a crucial function in tumor development and distant metastasis (7-10). Previous studies have indicated that inflammation is associated with the formation of the tumor microenvironment by inflammatory mediators, including vasoactive amines and cytokines (11-13). The C-reactive protein (CRP)/albumin (Alb) ratio is used as a novel inflammation-based prognostic indicator in multiple types of tumor. Previous studies have demonstrated the prognostic value of CRP/Alb ratio in colorectal (14) and esophageal cancer (15), hepatocellular carcinoma (16), and renal (17) and pancreatic cancer (18). Another important inflammatory marker is the neutrophil/lymphocyte ratio (NLR). NLR represents the balance between inflammatory activation and regulatory factors (19). Increased NLR may also serve as an independent prognostic risk factor in multiple types of cancer, including lung (20) and breast cancer (21), renal cell carcinoma (22), and ovarian cancer (23). The present

Correspondence to: Professor Wanli Liu, Department of Clinical Laboratory, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dong Feng Road East, Guangzhou, Guangdong 510060, P.R. China
E-mail: liuwanliandwang@163.com

*Contributed equally

Abbreviations: GC, gastric cancer; OS, overall survival; TNM, tumor-node-metastasis; CRP/Alb ratio, C-reactive protein/albumin ratio; NLR, neutrophil/lymphocyte ratio

Key words: gastric cancer, C-reactive protein, albumin, neutrophil, lymphocyte, prognosis

study evaluated the individual and combined prognostic value of CRP/Alb and NLR in Chinese patients with GC.

Patients and methods

Patients. The present study retrospectively reviewed the clinical data of 395 patients pathologically diagnosed with GC from Sun Yat-sen University Cancer Center between January 2010 and December 2010 (Guangzhou, China). The patients were classified and staged based on the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system (24). Patients without pathological diagnosis and laboratory test information on CRP, Alb, neutrophils and lymphocytes were excluded from analysis. The present study also excluded patients with other tumors, autoimmune diseases and those lost to follow-up. In total, 337 of the 395 patients reviewed were included for analysis in the present study. Of these, 237 (70.3%) were male and 100 (29.7%) were female (median age, 59; age range, 19-89). The information on CRP, Alb, neutrophils and lymphocytes was obtained from the test report from the Department of Clinical Laboratory at the Sun Yat-sen University Cancer Center. Other clinicopathological characteristics were collected through medical records.

Ethics statement. All patients provided written informed consent for the information to be used in the database of Sun Yat-sen University Cancer Center. The Ethics Committee at the Sun Yat-sen University Cancer Center approved the present study. The present study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

Statistical analysis. Data are expressed as the mean \pm standard deviation. The significance of association between the CRP/Alb ratio or NLR, and the clinicopathological characteristics were assessed using the χ^2 test. OS was defined as the time interval between diagnosis and mortality due to GC or the last follow-up. The optimal cut-off points for continuous prognostic indices were determined using the method reported by Budeczieš *et al* (25). Survival curves were constructed using the Kaplan-Meier method. Differences in survival were assessed using the log-rank test. The Cox proportional hazards regression model was used for univariate and multivariate analysis. The significant prognostic factors identified in univariate analysis were selected for multivariate analysis. All statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL, USA). A two-tailed $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 337 patients were included for analysis in the present study; however, some of the patients' data of tumor size, location and differentiation level were lost. Of the available data, 42 (12.5%), 49 (14.5%), 142 (42.1%) and 104 (30.9%) were staged I, II, III and IV, respectively. In addition, 89 (34.1%) patients had tumors < 4 cm, and 172 (65.9%) had primary tumors ≥ 4 cm. The present study identified that 185 (55.2%) and 104 (31.1%) patients with tumors located in the proximal and distal

stomach, respectively, while 46 (13.7%) exhibited tumors in other locations, including gastric stump cancer and linitis plastica. A total of 230 (70.1%) patients exhibited poorly or not differentiated tumors, 96 (29.3%) exhibited moderately differentiated tumors, and only 2 (0.6%) patients exhibited well-differentiated tumors.

Association between CRP/Alb ratio, NLR and clinicopathological characteristics. The association between CRP/Alb ratio and NLR, and clinicopathological characteristics was assessed (Table I). The CRP/Alb ratio ranged from 0.003-4.77 (median, 0.23), and NLR ranged from 0.47-23.00 (median, 2.95). For OS, the optimal cut-off values of the CRP/Alb ratio and NLR were 0.38 and 3.41, respectively. The present study revealed that high CRP/Alb ratio and NLR values were associated with increased tumor invasion (CRP/Alb, $P = 0.006$; NLR, $P = 0.005$), increased distant metastasis (CRP/Alb, $P < 0.001$; NLR, $P < 0.001$) and a more advanced TNM stage (CRP/Alb, $P < 0.001$; NLR, $P < 0.001$). In addition, a high NLR value was associated with increased tumor size ($P = 0.02$).

Prognostic value of the CRP/Alb ratio, NLR and OS. The median survival time for the patients was 29.77 months (range, 0.43-59.57 months). Survival analysis revealed that patients with a high CRP/Alb ratio were associated with a significantly decreased OS rate compared with those with a decreased CRP/Alb ratio ($P < 0.001$; Fig. 1). Similarly, patients with a high NLR value were associated with a significantly decreased OS rate compared with those with a low NLR ($P < 0.001$; Fig. 2). In univariate analysis, age ($P = 0.005$), tumor location ($P < 0.001$), TNM stage ($P < 0.001$), distant metastasis ($P < 0.001$), surgery ($P < 0.001$), CRP/Alb ratio ($P < 0.001$) and NLR ($P < 0.001$) were revealed to be significantly associated with OS. Multivariate analysis identified age ($P < 0.001$), TNM stage ($P < 0.001$), surgery ($P = 0.002$), CRP/Alb ratio ($P = 0.005$) and NLR ($P = 0.001$) as independent prognostic factors (Table II).

Prognostic value of the CRP/Alb ratio and NLR classification. According to the optimal cut-off values of the CRP/Alb ratio ($< 0.38 / \geq 0.38$) and NLR ($< 3.41 / \geq 3.41$), the present study classified the patients into subgroups: Group I, patients with increased CRP/Alb ratio (≥ 0.38) and NLR (≥ 3.41); group III, patients with decreased CRP/Alb ratio (< 0.38) and NLR (< 3.41); and group II, all remaining patients. Among the 337 patients, 29 (8.60%) patients were located in group I, 76 (22.55%) patients were located in group II and 232 (68.84%) patients were located in group III. The median OS values for patients in group I, II and III were 5.10, 17.80, and 46.50 months, respectively. Using univariate analysis, the present study identified that patients in group I exhibited the lowest OS of the subgroups ($P < 0.001$). Patients in group II [hazard ratio (HR), 95%; confidence interval (CI), 0.33 (0.19-0.57); $P < 0.001$] and group III [HR, 95%; CI, 0.25 (0.15-0.42); $P < 0.001$] exhibited significantly increased OS compared with patients in group I (Fig. 3; Table III). Univariate analysis revealed that age ($P = 0.005$), tumor location ($P < 0.001$), TNM stage ($P < 0.001$), distant metastasis ($P < 0.001$), surgery ($P < 0.001$), and CRP/Alb ratio and NLR classification ($P < 0.001$) were significant prognostic factors. Multivariate analysis also demonstrated that these

Table I. Association between the CRP/ALB ratio and NLR with clinicopathological characteristics in patients with gastric cancer.

Characteristic	CRP/ALB ratio			NLR		
	<0.3778 n, (%)	≥0.3778 n, (%)	P-value	<3.41 n, (%)	≥3.41 n, (%)	P-value
Sex			0.280			0.130
Male	195 (69.1)	42 (76.4)		176 (68.2)	61 (77.2)	
Female	87 (30.9)	13 (23.6)		82 (31.8)	18 (22.8)	
Age, years			0.290			0.180
≤59	140 (49.6)	23 (41.8)		130 (50.4)	33 (41.8)	
>59	142 (50.4)	32 (58.2)		128 (49.6)	46 (58.2)	
TNM stage ^b			<0.001 ^a			<0.001 ^a
I	40 (14.2)	2 (3.6)		40 (15.5)	2 (2.5)	
II	45 (16.0)	4 (7.3)		42 (16.3)	7 (8.9)	
III	126 (44.7)	16 (29.1)		117 (45.3)	25 (31.6)	
IV	71 (25.2)	33 (60.0)		59 (22.9)	45 (57.0)	
N stage ^b			0.600			0.180
N0	72 (30.1)	6 (25.0)		70 (31.3)	8 (20.5)	
N1+N2+N3	167 (69.9)	18 (75.0)		154 (68.8)	31 (79.5)	
T stage ^b			0.006 ^a			0.005 ^a
T1+T2+T3	80 (32.8)	2 (7.4)		77 (33.6)	5 (11.9)	
T4	164 (67.2)	25 (92.6)		152 (66.4)	37 (88.1)	
M stage ^b			<0.001 ^a			<0.001 ^a
M0	211 (74.8)	22 (40.0)		199 (77.1)	34 (43.0)	
M1	71 (25.2)	33 (60.0)		59 (22.4)	45 (57.0)	
Primary tumor size, cm			0.320			0.021 ^a
<4.0	83 (35.0)	6 (25.0)		82 (36.9)	7 (17.9)	
≥4.0	154 (65.0)	18 (75.0)		140 (63.1)	32 (82.1)	
Tumor location			0.230			0.070
Proximal	160 (57.1)	25 (45.5)		146 (56.8)	39 (50.0)	
Remote	84 (30.0)	20 (36.4)		82 (31.9)	22 (28.2)	
Other	36 (12.9)	10 (18.2)		29 (11.3)	17 (21.8)	
Degree of differentiation			0.590			0.390
Poorly/not differentiated	195 (70.9)	35 (66.0)		177 (69.4)	53 (72.6)	
Moderately differentiated	78 (28.4)	18 (34.0)		77 (30.2)	19 (26.0)	
Well-differentiated	2 (0.7)	0 (0.0)		1 (0.4)	1 (1.4)	

^aStatistically significant P-value. ^bAJCC. CRP, C-reactive protein; ALB, albumin; n, number of patients; TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer.

parameters, with the exception of tumor location, were significant prognostic factors. Notably, the CRP/Alb ratio and NLR classification ($P<0.001$) was identified as an independent prognostic factor in univariate and multivariate analyses (Table III).

Discussion

GC is a common malignant tumor of the upper digestive tract. In 2015, GC exhibited the second highest incidence and mortality rate among various types of cancer in China (1). In previous studies, plasma fibrinogen (26), α -fetoprotein (27), carcinoembryonic antigen-related cell adhesion molecule 5 (28) and the platelet/lymphocyte ratio (29) were

demonstrated to be prognostic indicators for GC with the same TNM stage. The levels of CRP, Alb, neutrophils and lymphocytes are all routinely tested in clinical practice, which means that data on these parameters are readily available. The present study revealed that CRP/Alb ratio and NLR served as independent prognostic factors for OS in patients with GC. The combination of these indexes was associated with significant prognostic value and may further stratify prognosis.

The association between inflammation and cancer is complex. During the inflammatory response, cytokines [e.g., interleukin (IL)-6] and chemokines (e.g., C-C motif chemokine ligand 2 and C-X-C motif chemokine ligand 8) are produced, which may activate signal transducer and activator

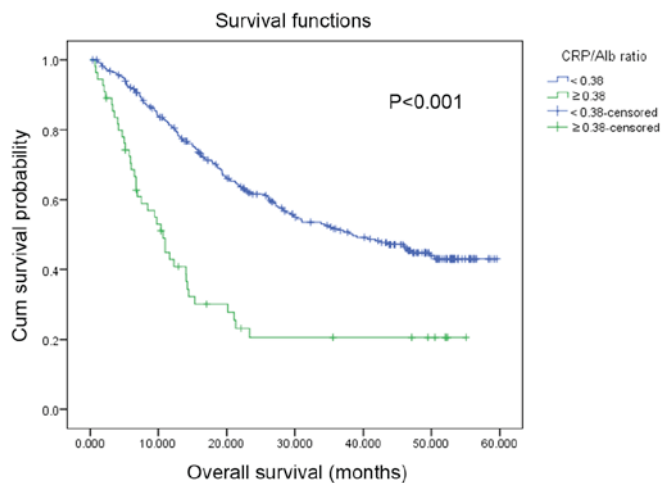


Figure 1. Prognostic value of the CRP/Alb ratio for overall survival in patients with gastric cancer. Patients with high CRP/Alb ratio value (≥ 0.38) had a significantly worse overall survival compared with those with low CRP/Alb ratio value (< 0.38). CRP, C-reactive protein; Alb, albumin; NLR, neutrophil/lymphocyte ratio.

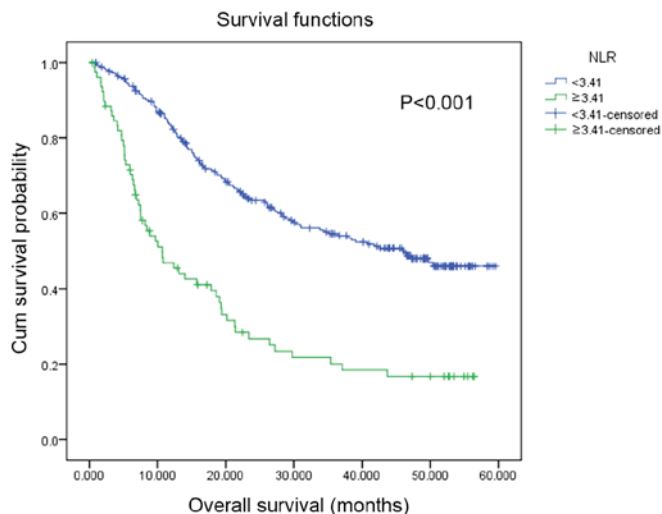


Figure 2. Prognostic value of the NLR for overall survival in patients with gastric cancer. Patients with a high NLR value (≥ 3.41) were associated with a significantly decreased overall survival compared with those with a low NLR value (< 3.41). NLR, neutrophil/lymphocyte ratio.

of transcription 3 and nuclear factor κ B, and recruit an increased number of inflammatory cells, including neutrophilic granulocytes and mononuclear macrophages, to the lesion site and thereby assist in forming an inflammatory microenvironment (13,30,31). The interaction between tumor cells and inflammatory factors may suppress the immunosurveillance of T and natural killer cells (32), enhance the permeability of blood and lymphatic vessels and degrade the extracellular matrix, thereby potentiating tumor development and metastasis (12,33). Furthermore, tumor cells may secrete inflammatory mediators and thereby assist in forming an inflammatory microenvironment (34).

CRP and Alb are produced by liver cells. CRP is an acute phase protein regulated by IL-6, tumor necrosis factor and other inflammatory factors (35). Therefore, CRP may

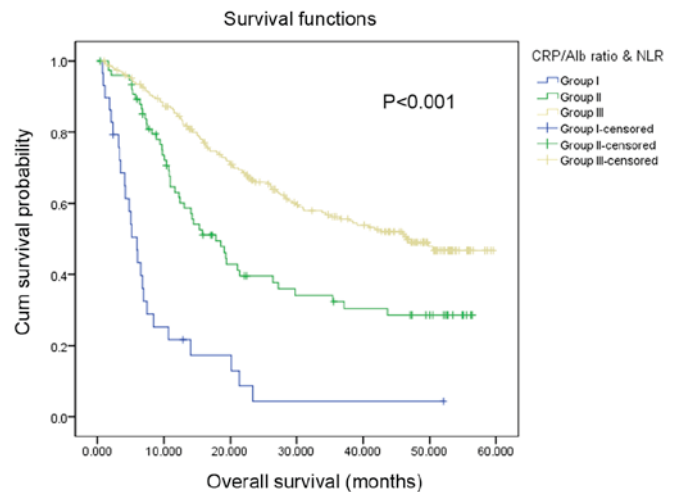


Figure 3. Prognostic value as determined by Kaplan-Meier curves of the combination of CRP/Alb ratio and NLR. All patients were classified into subgroups according to optimal cut-off values of the CRP/Alb ratio ($< 0.38/\geq 0.38$) and NLR ($< 3.41/\geq 3.41$). Patients with an increased CRP/Alb ratio and NLR were associated with decreased overall survival. Patients with decreased CRP/Alb ratio and NLR were associated with increased overall survival. Cum, cumulative; CRP, C-reactive protein; Alb, albumin; NLR, neutrophil/lymphocyte ratio.

indicate inflammation. Previous studies have demonstrated that an increased level of CRP may be associated with poorer prognosis in patients with tumors, including ovarian cancer, penile cancer and non-small cell lung cancer (36-38). In addition, malabsorption and malnutrition may be associated with decreased survival time in various tumors, including esophageal squamous cell carcinomas and endometrial cancer (39,40). In a previous study, Alb was used to estimate nutritional status. For patients with GC, protein digestion and absorption were decreased, whereas protein metabolism was increased, resulting in a negative nitrogen balance (18,39). The CRP/Alb ratio is a useful prognostic indicator that was initially used to identify patients with serious conditions on an acute medical ward by Fairclough *et al* (41). Subsequently, multiple studies have demonstrated that the CRP/Alb ratio exhibited prognostic value in numerous types of cancer (15-18,42). The present study revealed that a high CRP/Alb ratio indicated increased tumor invasion and metastasis and poorer prognosis compared with a low CRP/Alb ratio.

NLR serves as an index in routine blood tests. Multiple studies have confirmed that NLR is an easily available and reliable marker, which is associated with poor prognosis in various malignancies (19-23). The present study revealed that NLR was significantly associated with TNM stage, tumor invasion, tumor size, distant metastasis and poor prognosis, which was consistent with a previous study (43). The balance between the inflammatory and immune response is also reflected by NLR. Neutrophils contribute to inflammation by activating pro-angiogenic factors, including vascular endothelial growth factor or inflammatory cytokines (e.g., IL-1 β) (44,45). In addition, these neutrophils may also secrete agents that promote tumor cellular proliferation, angiogenesis, invasion and metastasis (46), and they may inhibit T cells (47). As important components of the non-specific and

Table II. Prognostic value of the CRP/ALB ratio and NLR for overall survival in patients with gastric cancer by univariate and multivariate analysis.

Characteristic	Univariate analysis		Multivariate analysis		
	N, (%)	P-value	Hazard ratio	95% CI	P-value
Sex		0.500			
Male	237 (70.3)				
Female	100 (29.7)				
Age, years		0.005 ^a			<0.001 ^a
≤59	163 (48.4)		1.00	Reference	
>59	174 (51.6)		1.92	1.39-2.65	
Tumor location		<0.001 ^a			
Proximal	185 (55.2)				
Remote	104 (31.0)				
Other	46 (13.7)				
Degree of differentiation		0.060			
Poorly or not differentiated	230 (70.1)				
Moderately differentiated	96 (29.3)				
Well-differentiated	2 (0.6)				
TNM stage ^b		<0.001 ^a			<0.001 ^a
I	42 (12.5)		1.00	Reference	
II	49 (14.5)		1.43	0.55-3.69	0.470
III	142 (42.1)		4.24	1.95-9.22	<0.001 ^a
IV	104 (30.9)		8.17	3.53-18.91	<0.001 ^a
Distant metastasis		<0.001 ^a			
No	233 (69.1)				
Yes	104 (30.9)				
Surgery		<0.001 ^a			0.002 ^a
No	74 (22.0)		1.00	Reference	
Yes	263 (78.0)		0.46	0.28-0.75	
CRP/ALB ratio		<0.001 ^a			0.005 ^a
<0.3778	282 (83.7)		1.00	Reference	
≥0.3778	55 (16.3)		1.78	1.20-2.65	
NLR		<0.001 ^a			0.001 ^a
<3.41	258 (76.6)		1.00	Reference	
≥3.41	79 (23.4)		1.74	1.25-2.44	

^aStatistically significant prognostic factor identified using univariate or multivariate analysis. ^bAJCC. The cut-off points for age, the CRP/ALB ratio, and NLR were determined using the method reported by Budczie *et al* (25). TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer; CI, confidence interval; CRP, C-reactive protein; ALB, albumin; NLR, neutrophil/lymphocyte ratio.

adaptive immune response, lymphocytes are able to destroy tumor cells via cytotoxic cells and cytokine secretion (48). A decreased lymphocyte count results in reduced tumor resistance (49). These mechanisms support the results of the present study.

The multivariate analysis of the present study demonstrated that the CRP/Alb ratio and NLR exhibited significant prognostic value in GC. In the present study, the patients were classified according to CRP/Alb ratio (<0.38/≥0.38) and NLR (<3.41/≥3.41). In groups I, II, and III, the median OS was 5.10, 17.80 and 46.50 months, respectively. The survival difference among the subgroups may be due to the CRP/Alb ratio and

NLR, which reflect a combination of inflammation, immune and nutrition status caused by tumor progression. Therefore, the combination of the CRP/Alb ratio and NLR was associated with significant prognostic value in GC.

Although the prognostic value of the CRP/Alb ratio and NLR in GC has been reported previously (42,50), to the best of our knowledge, the present study is the first to report that the combination of the CRP/Alb ratio and NLR is associated with significant prognostic value and may further stratify prognosis compared with using single indicators.

However, the present study has a number of limitations. The present study was a retrospective analysis, and the

Table III. Prognostic value of the CRP/ALB ratio and NLR for overall survival in patients with gastric cancer by univariate and multivariate analysis.

Characteristic	Univariate analysis		Multivariate analysis		
	N, (%)	P-value	Hazard ratio	95% confidence interval	P-value
Sex		0.500			
Male	237 (70.3)				
Female	100 (29.3)				
Age, years		0.005 ^a			<0.001
≤59	163 (48.4)		1.00	Reference	
>59	174 (51.6)		2.01	1.45-2.78	
Tumor location		<0.001 ^a			
Proximal	185 (55.2)				
Remote	104 (31.0)				
Other	46 (13.7)				
Degree of differentiation		0.060			
Poorly or not differentiated	230 (70.1)				
Moderately differentiated	96 (29.3)				
Well-differentiated	2 (0.6)				
TNM stage ^b		<0.001 ^a			<0.001 ^a
I	42 (12.5)		1.00	Reference	
II	49 (14.5)		1.40	0.54-3.61	0.500
III	142 (42.1)		4.38	2.01-9.51	<0.001 ^a
IV	104 (30.9)		8.50	3.68-19.63	<0.001 ^a
Distant metastasis		<0.001 ^a			
No	233 (69.1)				
Yes	104 (30.9)				
Surgery		<0.001 ^a			<0.001 ^a
No	74 (22.0)		1.00	Reference	
Yes	263 (78.0)		0.49	0.30-0.80	
CRP/ALB ratio and NLR classification		<0.001 ^a			<0.001 ^a
Group I	29 (8.6)		1.00	Reference	
Group II	76 (22.6)		0.33	0.19-0.57	<0.001 ^a
Group III	232 (68.8)		0.25	0.15-0.42	<0.001 ^a

^aStatistically significant prognostic factor identified using univariate or multivariate analysis. ^bAJCC. Group I, patients with increased CRP/ALB ratio (>0.3778) and NLR (>3.14); group III, patients with decreased CRP/ALB ratio (≤0.3778) and NLR (≤3.14); group II, all remaining patients. CRP, C-reactive protein; ALB, albumin; NLR, neutrophil/lymphocyte ratio; TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer.

conclusions require confirmation by perspective studies. Secondly, the present study did not use a uniform cut-off value for the CRP/Alb ratio and NLR. Therefore, different statistical methods may obtain different thresholds. However, the method used by the present study was based on R, which has been reliably used by other studies (15,51,52). To conclude, the present study revealed that the combination of the CRP/Alb ratio and NLR represents a potential inflammation-based prognostic marker. This marker was associated with invasive clinico-pathological characteristics and was able to predict prognosis in patients with GC. Larger, prospective studies are required to evaluate the results of the present study in the context of other types of malignancy.

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