

Original Article

Prognostic value of C-reactive protein/albumin ratio in patients receiving first-line palliative chemotherapy with unresectable stage IV gastric cancer

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Abstract: Background: A systemic inflammatory response is associated with poor prognosis of patients with advanced cancers. We investigated the prognostic value of the C-reactive protein/albumin (CRP/Alb) ratio in patients with metastatic gastric cancer. Methods: We retrospectively evaluated 258 patients with newly diagnosed metastatic gastric cancer. We investigated the correlations between the pretreatment CRP/Alb ratio and OS. We evaluated the prognostic value of the CRP/Alb ratio compared with other inflammation-based prognostic scores using the area under the curve (AUC) as follows: Glasgow Prognostic Score (GPS), modified GPS (mGPS), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). Results: Multivariate analysis demonstrated that only an elevated CRP/Alb ratio, GPS, and peritoneal metastasis were independent predictors of shorter OS. We determined the optimal cutoff value of the CRP/Alb ratio (0.5897), and found that a CRP/Alb ratio >0.5897 was associated with tumor progression. The AUC value of the CRP/Alb ratio was significantly higher compared with those of the GPS, mGPS, PLR, and MLR. There was a significant difference between the AUC value of the CRP/Alb ratio and other systemic inflammatory markers. Conclusions: The CRP/Alb ratio shows promise as an independent prognostic marker for patients with metastatic gastric cancer. The CRP/Alb ratio was more selective for patients with survival <6 months. The prognostic value of the CRP/Alb ratio must be validated by larger prospective studies.

Keywords: Gastric cancer, stage IV, CRP, albumin, systemic inflammation, prognostic score, overall survival

Introduction

Gastric cancer is the fourth most frequent malignancy and the second leading cause of cancer-related mortality [1]. The prognosis of patients with metastatic gastric cancer is very poor, and palliative chemotherapy for advanced or metastatic disease can improve survival and quality of life [2-4]. The 5-year survival rates for recurrent or metastatic gastric cancer range from 5% to 20% [5-7]. Despite frequently short and poor overall survival (OS), there is marked heterogeneity in the duration of survival. Therefore, efforts continue to identify prognostic factors related to survival [8, 9].

A growing body of evidence demonstrates that the outcomes of patients with cancer are determined not only by tumor-related factors but by

host-related factors as well, particularly the systemic inflammatory response [10, 11]. For example, cancer-related inflammation can influence cell proliferation, tumor-cell migration, invasion, metastasis, cell survival, and angiogenesis [12]. The systemic inflammatory response plays a major role in the progressive nutritional and functional decline of patients with cancer [13], and a systemic inflammatory response is associated with poor outcomes of patients with many types of cancer [14]. Evidence indicates that inflammation plays an important role in tumorigenesis, and an inflammatory microenvironment (e.g., angiogenesis, cytokine signaling) is an essential component of tumors [15].

C-reactive protein (CRP) is an acute-phase protein that is synthesized by hepatocytes, and its

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Table 1. Correlation of the CRP/Alb ratio with patients' baseline characteristics

Characteristic	Patients, n (%)		P value
	CRP/Alb \leq 0.5897	CRP/Alb $>$ 0.5897	
Sex			0.023*
Male	135 (67.8%)	49 (83.1%)	
Female	64 (32.2%)	10 (16.9%)	
Age (y)			0.809
$>$ 61.5	98 (49.2%)	28 (47.5%)	
\leq 61.5	101 (50.8%)	31 (52.5%)	
Location of primary tumor			0.128
Upper-third	80 (40.2%)	16 (27.1%)	
Middle-third	52 (26.1%)	22 (37.3%)	
Lower-third	67 (33.7%)	21 (35.6%)	
Lymphocytes			$<$ 0.001*
$>$ 1.565	95 (47.7%)	13 (22.0%)	
\leq 1.565	104 (52.3%)	46 (78.0%)	
Platelets			0.441
$>$ 310.5	35 (17.6%)	13 (22.0%)	
\leq 310.5	164 (82.4%)	46 (78.0%)	
Monocytes			0.045*
$>$ 0.365	135 (67.8%)	48 (81.4%)	
\leq 0.365	64 (32.2%)	11 (18.6%)	
Hemoglobin			0.001*
$>$ 115.5	116 (58.3%)	20 (33.9%)	
\leq 115.5	83 (41.7%)	39 (66.1%)	
Globulins			0.220
$>$ 30.75	67 (33.7%)	25 (42.4%)	
\leq 30.75	132 (66.3%)	34 (57.6%)	
CRP			$<$ 0.001*
CRP $>$ 10	25 (12.6%)	59 (100.0%)	
CRP \leq 10	174 (87.4%)	0 (0%)	
Alb			$<$ 0.001*
Alb $<$ 35	91 (45.7%)	51 (86.4%)	
Alb \geq 35	108 (54.3%)	8 (13.6%)	

*Significant differences between patients with CRP/Alb \leq 0.5897 and CRP/Alb $>$ 0.5897. CRP/Alb = C-reactive protein/albumin ratio, CRP = C-reactive protein, Alb = albumin. The cutoff values for age, neutrophils, lymphocytes, platelets, monocytes, hemoglobin, globulins, CRP, and Alb were determined as described in the Methods section.

levels in the circulation increase during the course of inflammatory diseases [16]. High CRP levels are common in patients with cancer [17], and advanced cancer is often associated with an inflammatory response [18]. Moreover, elevated levels of CRP predict shorter survival of patients with various cancers [8, 19, 20].

Observational studies suggest that low levels of serum albumin are associated with higher

cancer mortality rates. Serum albumin levels serve as an independent prognostic factor of survival of patients with cancers [21, 22] of the lung cancer [23], pancreas [24], gastrointestinal tract [25], colon and rectum [26], and breast [27]. Inflammation-based prognostic scores, including the Glasgow Prognostic Score (GPS), the modified GPS (mGPS), the neutrophil lymphocyte ratio (NLR), the platelet lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR) have prognostic value for many cancers [8, 28-31]. For example, the ratio of CRP to albumin (CRP/Alb) correlates with poor outcomes of patients with acute medical admissions and sepsis [32, 33].

Although the CRP/Alb ratio correlates with poor prognosis of patients with hepatocellular carcinoma [34], its significance for evaluating patients with metastatic gastric cancer is unknown. Therefore, our goal was to answer questions about the prognostic value of the CRP/Alb ratio for these patients as follows: 1. Does the ratio correlate with prognosis? 2. How does the ratio compare with other established inflammation-based prognostic scores such as the GPS, mGPS, PLR, and MLR? 3. Will the ratio contribute prognostic insights for

managing these cancer patients undergoing first-line chemotherapy?

Materials and methods

Study population and ethics

We conducted a retrospective review of the medical records acquired from the Medical Oncology Department of the Third Affiliated

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Table 2. Prognostic factors for overall survival identified using univariate and multivariate analyses

Characteristics	No. (%)	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Sex		0.900	0.668-1.213	0.489	0.799	0.577-1.107	0.178
Male	184 (71.3)						
Female	74 (28.7)						
Age (yr)		0.814	0.624-1.063	0.131	0.997	0.984-1.011	0.718
>61.5	126 (48.8)						
≤61.5	132 (51.2)						
Location of primary tumor		1.102	0.939-1.293	0.236	1.062	0.888-1.271	0.510
Upper-third	96 (37.2)						
Middle-third	74 (28.7)						
Lower-third	88 (34.1)						
Peritoneal metastasis		0.563	0.407-0.778	<0.001*	0.597	0.418-0.853	0.005*
Yes	53 (20.5)						
No	205 (79.5)						
Hemoglobin		1.456	1.115-1.900	0.006*	0.999	0.992-1.005	0.710
>115.5	136 (52.7)						
≤115.5	122 (47.3)						
Globulins		1.072	0.804-1.429	0.636	1.016	0.988-1.044	0.262
>30.75	92 (35.7)						
≤30.75	166 (64.3)						
CRP/Alb		2.006	1.476-2.726	<0.001*	1.333	1.028-1.729	0.030*
≤0.5897	199 (77.1)						
>0.5897	59 (22.9)						
GPS		1.460	1.238-1.723	<0.001*	1.572	1.091-2.265	0.015*
GPS = 0	100 (38.8)						
GPS = 1	90 (34.9)						
GPS = 2	68 (26.4)						
mGPS		1.325	1.142-1.538	<0.001*	0.750	0.535-1.050	0.094
mGPS = 0	174 (67.4)						
mGPS = 1	16 (6.2)						
mGPS = 2	68 (26.4)						
PLR		0.657	0.489-0.882	0.005*	1.000	0.999-1.002	0.690
>117.3603	177 (68.6)						
≤117.3603	81 (31.4)						
MLR		0.638	0.487-0.834	0.001*	0.971	0.463-2.036	0.939
>0.3208	131 (50.8)						
≤0.3208	127 (49.2)						

*Statistically significant differences determined using univariate and multivariate analyses. HR = hazard ratio, CI = confidence interval, CRP/Alb = C-reactive protein/albumin ratio, GPS = Glasgow Prognostic Score, mGPS = modified Glasgow Prognostic Score, PLR = platelet lymphocyte ratio, MLR = monocyte-to-lymphocyte ratio. The cutoff values for age (y), hemoglobin, globulins, CRP/Alb, GPS, mGPS, PLR, and MLR were determined as described in the Methods section.

Hospital, Soochow University, Changzhou, China of 258 patients with first diagnosed metastasis gastric cancer from January 1, 2010 to August 30, 2015. Pathological diagnoses were confirmed, and patients without a pathological

diagnosis were excluded. Patients were excluded if they had an infection or inflammatory disease for approximately 1 month, an autoimmune disease, and if data were unavailable regarding prognostic factors (**Tables 1 and 2**).

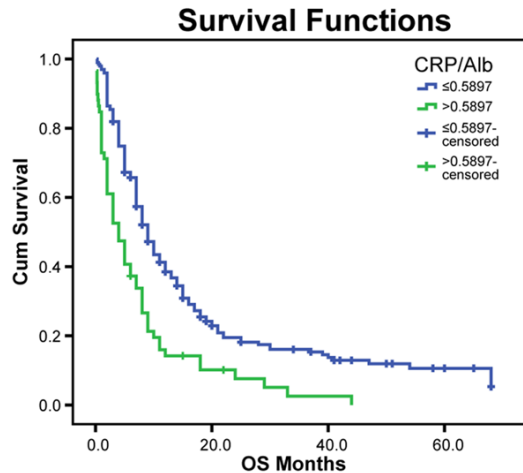


Figure 1. The prognostic value of the CRP/Alb ratio determined using Kaplan-Meier analysis. A lower CRP/Alb ratio (≤ 0.5897) was associated with significant better OS ($P < 0.001$). CRP/Alb = C-reactive protein/albumin ratio, OS = overall survival.

Patients without pretreatment information about inflammation-based prognostic indicators (**Tables 1** and **2**) were excluded as well as those who underwent previous surgery, radiotherapy, or chemotherapy at other hospitals. We excluded patients lost to follow-up as well as patients who died of causes unrelated to their cancer. The 258 patients who met the inclusion criteria were enrolled in our study. The clinical information and patients' pretreatment inflammation-based indexes were retrospectively collected from January 1, 2010 to August 30, 2015. Every patient provided written informed consent before participating in the study. The Research Ethics Committee of the Third Affiliated Hospital, Soochow University approved this study, which complied with the tenets of the World Medical Association's (most recently revised) Declaration of Helsinki.

Patients' characteristics

Tumors were staged according to the Seventh Edition of the American Joint Committee on Cancer tumor-nodes-metastasis staging system [35]. Gastric cancers were classified according to their location in the upper-third, middle-third, or lower-third of the gastrointestinal tract. Data regarding potential prognostic factors included pretreatment, sex, age, location of the primary tumor, peritoneal metastasis, globulins, neutrophils, lymphocytes, platelet, monocyte, hemoglobin, CRP, albumin, and

survival times. Blood samples were obtained within 1 week before treatment to measure globulins, lymphocytes, platelets, monocytes, hemoglobin, CRP, and albumin.

Definitions of inflammation-based prognostic scores

The inflammation-based prognostic scores were defined and calculated as follows: The CRP/Alb ratio was defined as the serum CRP level divided by the serum Alb level (CRP mg/L/albumin g/L) [32]. The GPS was calculated using CRP and Alb with standard thresholds (>10 mg/L, CRP; >35 g/L, Alb). Patients were assigned the scores as follows: Score = 2, CRP >10 mg/L and Alb >35 g/L; Score = 1, CRP >10 mg/L or Alb >35 g/L; Score = 0, neither of these abnormalities [36]. The scores for the mGPS were assigned as follows: Score = 0, CRP ≤ 10 mg/L; Score = 1, CRP >10 mg/L and albumin ≥ 35 g/L; Score = 2, CRP >10 mg/L and albumin ≤ 35 g/L [37]. All calculations of inflammation-based prognostic scores were calculated before patients were administered chemotherapy. The systemic inflammation scores included the CRP/Alb, GPS, mGPS, PLR, and MLR.

Treatment and follow-up

Overall survival was calculated from the date of first diagnosis to the date of death or last follow-up. Follow-up schedules were established and applied according to the National Comprehensive Cancer Network Clinical Practice Guidelines [38]. The last follow-up date was October 30, 2015. All patients received chemotherapy.

Statistical analysis

Differences in patients' baseline and clinic parameters between groups were evaluated using the χ^2 test according to the types of data and comparisons. OS curves were generated using the Kaplan-Meier method, and differences were evaluated using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Correlations with variables (sex, age, location of primary tumor, peritoneal metastasis, hemoglobin, globulin, CRP/Alb, GPS, mGPS, PLR, and MLR) were evaluated using univariate or multivariate analysis. The

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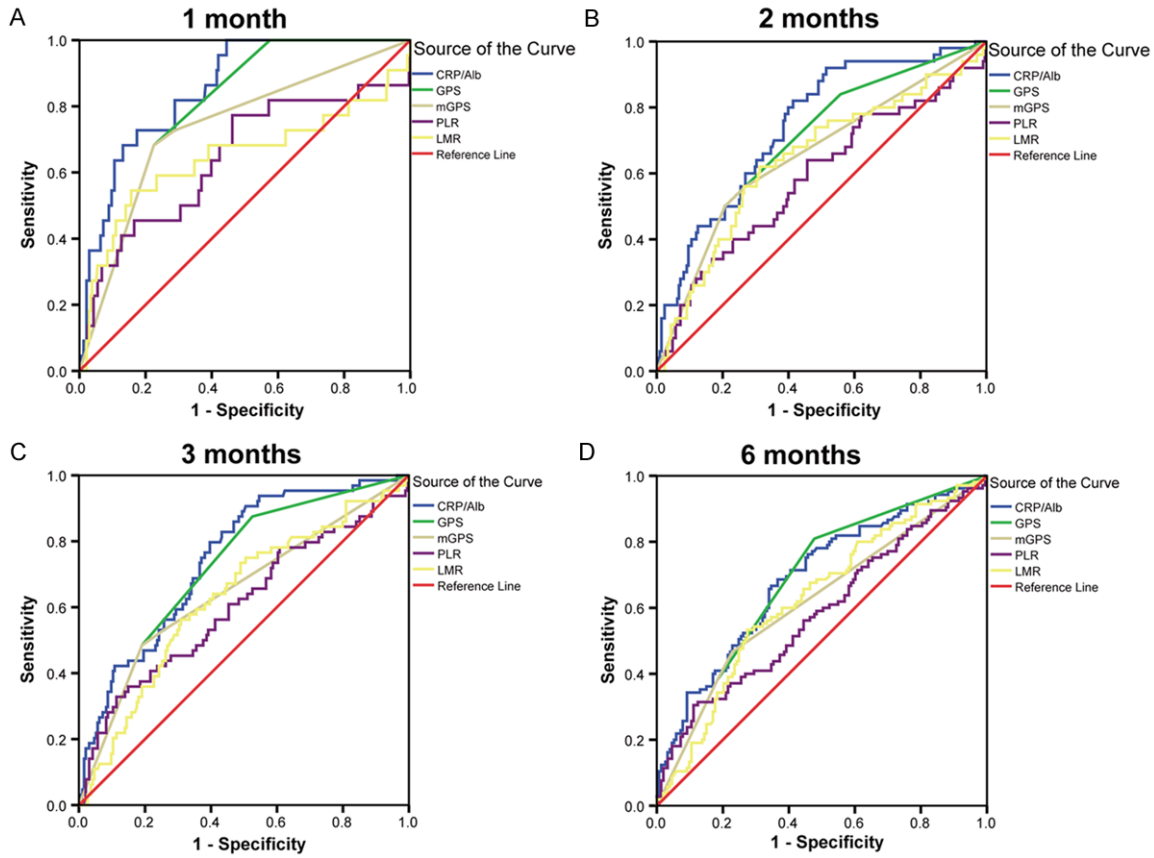


Figure 2. The ROC curves of inflammation-based prognostic indexes at the 1-, 2-, 3-, and 6-month follow-up examinations. Shown are the ROC curves of the CRP/alb ratio (continuous), GPS (categorical), mGPS (categorical), PLR (continuous), and MLR (continuous) for survival.

hazard ratio (HR) and 95% confidence interval (CI) were computed using the Cox proportional hazards regression model. Statistically significant prognostic variables identified using univariate analysis were selected for multivariate analysis using the forward stepwise method. If a continuous variable met the assumption of linearity in the logit, the variable was categorized by generating a receiver operating characteristic (ROC) curve to identify the optimal cut-off value.

Statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL USA). A two-tailed P value $<.05$ was considered statistically significant. To evaluate the discriminatory ability of the inflammation-based prognostic scores, ROCs were generated, and the areas under the curves (AUCs) were compared. The statistical significance of the differences between AUCs was compared using MedCalc software (Version 11.4.2.0).

Results

The relationships between the CRP/Alb ratio and each of the patients' clinic characteristics are shown in **Table 1**. Patients with an elevated CRP/Alb ratio were more likely male ($P = 0.023$) and had the clinical values as follows: higher number of monocytes ($P = .045$), higher level of CRP ($P < .001$), lower number of lymphocytes ($P < .001$), lower level of hemoglobin ($P = .001$) and Alb ($P < .001$) (**Table 1**). The median age of the 258 patients was 61.0 years (range, 21-75 years), and 184 (71.3%) patients were male. There were 96 (37.25%) patients with tumors located within the upper-third, 74 (28.7%) with tumors located within the middle-third, and 88 (34.1%) patients with tumors located within the lower-third of the gastrointestinal tract. All patients were classified as stage IV, and there were 53 (20.5%) patients with peritoneal metastasis. At the last follow-up, 218 (84.5%) patients were deceased. The median follow-up

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Table 3. Discriminatory abilities of prognostic scores according to the AUCs at 1, 2, 3, and 6 months

Time of follow-up	AUC	95% CI	P value	Significance of comparison §P' value
1-month follow-up				
CRP/Alb (continuous)	0.853	0.785-0.921	<0.001*	-
GPS	0.796	0.722-0.870	<0.001*	P' = 0.0006*
mGPS	0.736	0.621-0.851	<0.001*	P' < 0.0001*
PLR (continuous)	0.642	0.501-0.783	0.027*	P' = 0.0092*
MLR (continuous)	0.645	0.490-0.799	0.025*	P' = 0.0101*
2-month follow-up				
CRP/Alb (continuous)	0.745	0.671-0.818	<0.001*	-
GPS	0.694	0.613-0.774	<0.001*	P' = 0.0311*
mGPS	0.655	0.566-0.744	0.001*	P' = 0.0002*
PLR (continuous)	0.585	0.490-0.679	0.063	P' = 0.0028*
MLR (continuous)	0.642	0.552-0.732	0.002*	P' = 0.0604
3-month follow-up				
CRP/Alb (continuous)	0.746	0.680-0.812	<0.001*	-
GPS	0.719	0.649-0.788	<0.001*	P' = 0.1988
mGPS	0.649	0.567-0.730	<0.001*	P' < 0.0001*
PLR (continuous)	0.605	0.520-0.690	0.012*	P' = 0.0038*
MLR (continuous)	0.629	0.549-0.708	0.002*	P' = 0.0139*
6-month follow-up				
CRP/Alb (continuous)	0.687	0.621-0.753	<0.001*	-
GPS	0.683	0.617-0.749	<0.001*	P' = 0.8531
mGPS	0.620	0.549-0.691	0.001*	P' = 0.0010*
PLR (continuous)	0.584	0.512-0.656	0.022*	P' = 0.0219*
MLR (continuous)	0.627	0.558-0.696	0.001*	P' = 0.1347

*Significant P values of ROC curves analysis of systemic inflammation scores. ROC = receiver operating characteristics, AUC = area under the curves, CI = confidence interval, CRP/Alb = the C-reactive protein/Albumin ratio, GPS = Glasgow Prognostic Score, mGPS = modified Glasgow Prognostic Score, PLR = platelet lymphocyte ratio, MLR = the monocyte-to-lymphocyte ratio. §Comparisons of AUC values between the CRP/Alb ratio and other inflammation-based prognostic factors using the z-test method. A two-tailed P value < .05 was considered statistically significant. Significant differences are indicated by the asterisks.

period was 7.0 months (range, 0.2-68.0 months) (**Table 2**).

According to previous studies [39, 40], the accepted optimal cutoff values of albumin and CRP levels are lower or higher than the normal value, respectively. ROC curve analysis was performed to determine the optimal cutoff values for age, neutrophils, lymphocytes, platelets, monocytes, hemoglobin, globulins, CRP/Alb, PLR, and MLR (**Table 1**). The optimal cutoff value for the CRP/Alb ratio = 0.5897 for OS. According to the cutoff level, patients were divided into the groups as follows: 1) ≤ 0.5897 , n = 199 (77.1%) and 2) > 0.5897 , n = 59 (22.9%).

The 1-, 2-, 3-, and 6-month OS of patients with CRP/Alb ratios ≤ 0.5897 were 97%, 86.4%, 81.9%, and 65.7%, respectively. OS was significantly higher at these times compared with those of patients with a CRP/Alb ratio > 0.5897 (72.9%, 61%, 52.5%, and 37.3%, respectively). The median OS of patients with a CRP/Alb ratio ≤ 0.5897 was 9.0 months (7.485-10.515). The median survival rates were significantly higher compared with patients with CRP/Alb ratios > 0.5897 (4.0 months; range, 2.121-5.879; ($P < 0.001$)) (**Figure 1**).

Prognostic factors associated with OS were identified using univariate and multivariate analyses (**Table 2**). The systemic inflammation scores included CRP/Alb, GPS, mGPS, PLR, and MLR. Significant prognostic indexes identified by univariate analysis included peritoneal metastasis, hemoglobin, CRP/Alb, GPS, mGPS, PLR, and MLR (**Table 2**). These variables were selected for multivariate analysis using a forward stepwise method, and three indexes were identified as independent

prognostic factors for OS as follows: CRP/Alb (HR = 1.333; 95% CI, 1.028-1.729, $P = 0.030$), GPS (HR = 1.572; 95% CI, 1.091-2.265, $P = 0.015$), and peritoneal metastasis (HR = 0.597; 95% CI, 0.418-0.853, $P = 0.005$) (**Table 2**).

To compare the discriminatory ability of the CRP/Alb ratio with those of other established inflammation-based prognostic indexes, we generated ROC curves for survival status at different follow-up times and compared the differences of the estimated AUCs (**Figure 2; Table 3**). At follow-up examinations conducted 1, 2, 3, and 6 months, the AUC values of the CRP/Alb ratios were significantly higher compared with

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Table 4. Correlation of the CRP/Alb ratio with GPS

Characteristic	Patients n, (%)		P value
	CRP/Alb \leq 0.5897	CRP/Alb $>$ 0.5897	
GPS			$<$ 0.001*
GPS = 0	100	0	
GPS = 1	82	8	
GPS = 2	17	51	

*Statistically significant differences of the distribution between patients with CRP/Alb ratios \leq 0.5897 and $>$ 0.5897. CRP/Alb = C-reactive protein/albumin ratio, GPS = Glasgow Prognostic Score.

those of the GPS, mGPS, PLR, and MLR. The AUC values for the CRP/Alb ratio (continuous) were 0.853, 0.745, 0.746, and 0.687 at 1, 2, 3, and 6 months, respectively.

At 3 months, there were no significant differences in AUC values between the CRP/Alb ratio and GPS, although there was a significant difference between the CRP/Alb ratio and mGPS, PLR, or MLR. ROC analysis revealed that the AUC values for the CRP/Alb ratio (continuous) at 6 months were not statistically significant different from the GPS. The AUC values of the CRP/Alb ratio were higher compared with those of the mGPS and PLR scores at 6 months (**Table 3**). After a longer follow-up, there was a decrease in the discriminatory ability of all the inflammation-based scores. The ROC curves of the inflammation-based prognostic indexes are shown in **Figure 2**.

The CRP/Alb group was divided into the groups as follows (3-month follow-up): 1) CRP/Alb \leq 0.5897 (n = 199), 81.9% survival and 2) CRP/Alb $>$ 0.5897 (n = 59), 52.5% survival. When patients were classified according to GPS score (3-month follow-up), there were 100 patients with a GPS = 0, 92% survival; 90 patients with a GPS score = 1, 72.2% survival; and 68 patients with a GPS score = 2, 54.4% survival. There was a significant association between the CRP/Alb ratio (\leq 0.5897 vs. $>$ 0.5897) and the GPS. The CRP/Alb (continuous) was associated with the GPS ($P < .001$). Interestingly, the CRP/Alb was \leq 0.5897 for patients with a GPS score = 0 (**Table 4**).

The patients were divided into three groups according to GPS scores. Compared with GPS, the inflammation index of the CRP/Alb allowed us to divide patients into two groups, indicating that comparing the CRP/Alb cutoff value to that

of the GPS may select for patients with shorter survival. Further, it is easy for physicians to divide patients into two groups by applying the CRP/Alb ratio.

Discussion

Here, we demonstrate the prognostic value of the CRP/Alb ratio and the relationships between systemic inflammatory markers and OS of patients with metastatic gastric cancer receiving first-line palliative chemotherapy. Our most significant finding was that we predicted survival when we divided patients with metastatic gastric cancer into two groups according to the cutoff value of the CRP/Alb ratio. Specifically, prognosis was worse for patients with a higher CRP/Alb ratio as follows: CRP/Alb $>$ 0.5897, 52.5% of patients survived for 3 months, 37.3% of patients survived for 6 months. In contrast, CRP/Alb \leq 0.5897, 81.9% of patients survived for 3 months, 65.7% of patients survived for 6 months.

Our data are consistent with those reported by others that the optimal cutoff value of the CRP/Alb ratio predicts long-term survival of patients with operable esophageal squamous cell carcinoma [41]. Moreover, we hypothesized that the CRP/Alb ratio predicts shorter survival of patients with metastatic gastric cancer if it is combined with the inflammation index. When patients were diagnosed with metastatic gastric cancer, we predicted that they will survive for $<$ 6 months if CRP/Alb $>$ 0.5897. The CRP/Alb ratio is associated with an aggressive tumor phenotype [34, 41]. Therefore, patients with an elevated CRP/Alb ratio may require more aggressive adjuvant chemotherapy or additional active therapy.

Several mechanisms were proposed to explain the relationships between an inflammatory response and cancer progression [12, 42-44]. For example, tumor invasion or growth may induce tissue inflammation because of tumor hypoxia and necrosis or local tissue damage. Moreover, cancer cells, tumor-associated leukocytes, or both may induce the production of inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8 as well as vascular endothelial growth factor. These inflammatory cytokines and chemokines facili-

tate invasion by tumors as well as their growth, metastasis and associated angiogenesis, subversion of the host immune response, and resistance to cytotoxic drugs [12, 42-44]. It is generally accepted that cancer-associated inflammation is modulated by cancer and host stromal cells as well as by their interactions [18].

The liberation of multiple proinflammatory cytokines from the tumor environment induces CRP synthesis by the liver and other tissues [45]. CRP is a nonspecific but sensitive marker of a systemic inflammatory response, which might be expressed in selected tumor cells [46]. There is strong evidence that elevated CRP levels influence the growth and progression of cancers [47-49]. Specifically, evidence indicates that an elevated CRP level is a reliable indicator of poor prognosis for certain malignancies such as colorectal cancers, melanoma, non-Hodgkin lymphoma, prostate cancer, lung cancer, and ovarian cancer [14, 50, 51].

The mechanism that determines the influence of a systemic inflammatory response on tumor progression and survival is unknown. It is known, however, that an elevated systemic inflammatory response is associated with a poor local immune response to the tumor, leading to increased lymphatic metastasis [52]. Further, the presence of a systemic inflammatory response and the associated nutritional decline may influence patients' tolerance and compliance with treatment [53, 54].

Hypoalbuminemia is often secondary to an ongoing systemic inflammatory response [55, 56], and serum albumin levels are not only a window into a patient's nutritional status but serve as a useful marker for predicting the patient's prognosis [8, 57]. Several studies demonstrate that low albumin levels are significantly associated with poorer survival in patients with gastric cancer [57, 58]. Moreover, the presence of a systemic inflammatory response, indicated by elevated CRP levels, accompanies a decrease in serum albumin levels and progressive loss of weight and lean tissue, which diminish performance status and increase mortality of patients with cancer [59, 60].

Accumulating evidence clarifies the role of inflammation-based prognostic scores [8,

28-30, 59, 61-63], including the GPS, mGPS, and PLR for predicting the survival of patients with cancer. For example, the LMR is a useful prognostic marker for patients with metastatic colorectal cancer as well as those with small-cell lung cancer [31, 64]. Neutrophilia induces the secretion of vascular endothelial growth factor and accelerates tumor development, and lymphocytopenia reflects impairment of the host immune response to the tumor [65].

The CRP/Alb ratio is an independent marker for mortality of patients with sepsis and provides a higher accuracy than CRP values alone [32]. To our knowledge, only two studies demonstrate the relationship between CRP/Alb ratio and cancer-specific survival [34, 41]. However, the prognostic value of the CRP/Alb ratio of patients with metastasis gastric cancer is unknown. Therefore, this is the first study, to our knowledge, to show that the CRP/Alb ratio serves as a significant prognostic marker for patients with metastasis cancer.

According to a study of patients in the early and late stages of disease who were treated with curative or noncurative intent, the CRP/Alb ratio may serve as well as an independent prognostic marker for patients with hepatocellular carcinoma and may provide comparable prognostic ability compared with those of other established inflammation-based prognostic scores [34]. Another study found that the CRP/Alb ratio is an independent prognostic factor of survival of patients with operable esophageal squamous cell carcinoma [41].

The CRP/Alb ratio can serve as a novel inflammation-based prognostic score to predict survival of patients with hepatocellular carcinoma [34]. Our present study demonstrates that the CRP/Alb ratio, using a cutoff value of 0.5897, was a sensitive prognostic predictor of survival of patients with metastatic gastric cancer. To the best of our knowledge, this is the first study to identify the CRP/Alb ratio as a prognostic marker of shorter survival (<6 months) for patients with metastatic gastric cancer. In particular, this information has highly significant implications for managing patients. During 9 weeks of chemotherapy administered to patients with colorectal cancer, supplementation with eicosapentaenoic and docosahexaenoic acids in fish oil decreases the CRP/Alb ratio and prevents weight loss [66]. In the future, in com-

ination with our present results, nutritional support will likely reduce the CRP/Alb ratio and lengthen the survival of patients with advanced gastric cancer.

The CRP/Alb ratio is particularly suitable for managing patients with metastatic gastric cancer because it is an effective, simple, readily available, and inexpensive prognostic marker. Therefore, incorporating determination of the CRP/Alb into routine clinical practice will likely reduce the worldwide health burden imposed by metastatic gastric cancer.

There are several limitations of this study. For example, treatments differed and included chemotherapy and palliative radiotherapy. Further, we did not study the differences in the course of chemotherapy such as dose and adverse events. Other potential limitations of this study include its retrospective design, small sample size, and it was a single-center study. Therefore, future research, particularly prospective multi-center clinical trials, is warranted to validate our present findings.

Conclusions

We show here for the first time that the CRP/Alb ratio can provide significant prognostic value for patients receiving first-line chemotherapy for metastatic gastric cancer. Moreover, the prognostic power of the CRP/Alb ratio rivals or surpasses those of established inflammation-based prognostic scores, particularly for predicting patients who will survive for <6 months. When patients were diagnosed with metastatic gastric cancer, we predicted that they may survive <6 months if CRP/Alb>0.5897. We show as well that univariate analysis identified the CRP/Alb ratio; peritoneal metastasis; hemoglobin levels; and the scores for GPS, mGPS, PLR, and MLR as significant prognostic indexes. Further, multivariate analysis identified CRP/Alb, GPS, and peritoneal metastasis as independent prognostic factors for OS. Because of the potential value of the CRP/Alb ratio for managing patients with metastatic gastrointestinal cancer, further prospective studies of larger patient populations are clearly warranted. Studies that focus on the mechanisms of tumor-related inflammation involving CRP may provide new insights into preventing and managing a devastating disease.

Disclosure of conflict of interest

None.

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