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Original Article

C-reactive protein/albumin ratio as a predictor of survival of metastatic colorectal cancer patients receiving chemotherapy

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Abstract: Preoperative C-reactive protein/albumin (CRP/Alb) ratio has been reported to be an independent prognostic marker in patients with hepatocellular carcinoma. This retrospective study assessed whether CRP/Alb ratio was prognostic in 148 patients newly diagnosed with metastatic colorectal cancer. CRP/Alb ratio was correlated with pre-treatment baseline characteristics. Receiver operating characteristic (ROC) curves assessed survival at 6 and 12 months, with areas under the curve for CRP/Alb compared with those of inflammation-based prognostic scores, including Glasgow Prognostic Score (GPS), modified GPS, neutrophil-to-lymphocyte ratio (NPR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). The optimal CRP/Alb cut-off was 0.6712, with higher CRP/Alb significantly associated with greater age ($P = 0.035$); higher neutrophil ($P < 0.001$), platelet ($P = 0.016$) and monocyte ($P = 0.001$) counts; higher CRP ($P < 0.001$); and lower lymphocyte counts ($P = 0.038$) hemoglobin ($P = 0.001$) and Alb ($P < 0.001$). The CRP/Alb ratio had higher AUC values at 6 and 12 months than corresponding GPS, mGPS, NPR, PLR, and MLR. AUCs for CRP/Alb ratio differed significantly from mGPS, NLR, PLR and MLR at 6 and 12 months. Six-month survival rates in patients with CRP/Alb ≤ 0.6712 and > 0.6712 were 91.7% and 44.5%, respectively. These findings, showing that the CRP/Alb ratio is a better predictor of 6 month survival rates than indicators of systemic inflammation, including GPS, mGPS, NLR, PLR, and MLR, in patients with metastatic colorectal cancer, suggest that patients with a higher CRP/Alb ratio may require more aggressive treatment. Prospective multicenter studies are required to confirm the prognostic value of the CRP/Alb ratio.

Keywords: Metastatic, colorectal cancer, C-reactive protein, albumin, inflammation-based prognostic score, survival

Introduction

Colorectal cancer (CRC) accounts for 8%-9% of all cancers and is the second most frequent cause of cancer-related deaths in Western countries [1]. In 2014, there were an estimated 136,830 individuals newly diagnosed with colorectal cancer and 50,310 colorectal cancer deaths in the United States [2]. Approximately 20% of patients with colorectal cancer (CRC) present with stage IV disease at the time of diagnosis [3]. The median survival of patients with unresectable stage IV disease who receive best supportive care without chemotherapy is approximately 6 to 8 months [4]. The recent development of chemotherapeutic and molecular targeting agents has markedly improved median survival to almost 24 months [5-7]. However, some patients have a poorer prognosis due to rapid tumor growth and/or the ineffectiveness of chemotherapy. As stage IV colorectal cancer is a very broad disease category, it is difficult to predict patient prognosis based only on TNM classification [8]. Determining the prognostic factors in patients with stage IV colorectal cancer may identify patients at higher risk for poorer outcomes, thus enabling more aggressive therapy.

Systemic inflammatory responses play an important role in carcinogenesis and tumor progression [9-11]. The mechanism by which inflammation regulates tumor behavior and host status is complicated. For example, inter-

leukin (IL)-6 may induce the production of C-reactive protein (CRP), a nonspecific acute phase response protein [12], and activate STAT3 and NF-κB, preventing apoptosis and promoting the proliferation of malignant cells [13].

CRP is regarded as a markers of systemic inflammatory responses [14]. Other inflammation-based scores, including the Glasgow Prognostic Score (GPS), the modified GPS (mGPS), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR), have been reported to have prognostic significance in many types of cancers [15-21]. Recently, a new index, preoperative CRP/albumin (CRP/Alb) ratio, has been reported to be independently prognostic of survival in patients with hepatocellular carcinoma [22]. This study was therefore designed to determine whether the CRP/Alb ratio was also prognostic of survival in Chinese patients with metastatic colorectal cancer. This retrospective cohort analysis also compared the prognostic abilities of CRP/Alb with those of other inflammation-based prognostic scores, including GPS, mGPS, NLR, PLR, and LMR.

Materials and methods

Study population and ethics

The medical records of all patients newly diagnosed with metastasis colorectal cancer from January 1, 2010, to August 30, 2015, at the Medical Oncology Department of the Third Affiliated Hospital, Soochow University in Changzhou, China, were retrospectively evaluated. Pathological diagnoses were carefully reviewed. Patients who had received chemotherapy, radiotherapy or surgery at other hospitals before referral to our hospital, patients without pathological diagnoses, and patients without pretreatment information on inflammation-based prognostic indicators were excluded. Patients lost to follow-up; those who died of non-cancer causes; those with infections or inflammatory diseases for at least one month or immune system related diseases; and patients missing data on potential prognostic factors were also excluded. Finally, 148 patients were enrolled in this study. Their prospectively collected clinical information and pretreatment inflammation-based indices were retrospectively evaluated.

All patients provided written informed consent before inclusion. This study complied with the standards of the Declaration of Helsinki and was approved by the research ethics committee of the Third Affiliated Hospital of Soochow University.

Measurement of tumor-related characteristics

Demographic and pre-treatment clinical characteristics evaluated included patient sex and age; location of the primary tumor (colon or rectum); tumor stage according to the seventh edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) system [23] and number of metastases. Blood samples were obtained within 1 week prior to treatment to measure globulin, hemoglobin, CRP and albumin concentrations; and neutrophil, lymphocyte, platelet, and monocyte counts.

Definitions of inflammation-based prognostic scores

The GPS was calculated from CRP and Alb concentrations using standard thresholds. Patients with both a CRP level > 10 mg/l and an Alb level < 35 g/l were categorized as having a score of 2; those with one of these abnormalities were categorized as having a score of 1; and those with neither were categorized as having a score of 0 [24]. According to the mGPS, patients with a CRP level ≤ 10 mg/L were allocated a score of 0; those with both CRP > 10 mg/L and albumin ≥ 35 g/L were allocated a score of 1; and those with both CRP > 10 mg/L and albumin < 35 g/L were allocated a score of 2 [25]. NLR, PLR, and LMR were calculated as described [25, 26]. The CRP/Alb ratio was defined as serum CRP (mg/L) divided by serum Alb (g/L) [27].

Treatment and follow-up of patients

Overall survival (OS) was calculated from the date of initial diagnosis to the date of death or last follow-up. Patients were treated and followed-up according to National Comprehensive Cancer Network (NCCN) Clinical Practice guidelines. The last follow-up date was October 30, 2015. Patients with incurable disease continued to attend clinics or be hospitalized. All patients received chemotherapy.

Statistical analysis

Between groups differences in demographic and clinical parameters were evaluated by χ^2

Table 1. Correlations between CRP/Alb ratio and baseline characteristics of patients

Characteristic	No. of Patients (%)		*P* value
	CRP/Alb ≤ 0.6712	CRP/Alb > 0.6712	
Sex			0.346
Male	65 (63.1%)	32 (71.1%)	
Female	38 (36.9%)	13 (28.9%)	
Age (yr)			0.035*
> 69.5	20 (19.4%)	16 (35.6%)	
≤ 69.5	83 (80.6%)	29 (64.4%)	
Location of primary tumor			0.087
Colon	68 (66.0%)	36 (80.0%)	
Rectum	35 (34.0%)	9 (20.0%)	
Neutrophils (× 10^9/L)			< 0.001*
> 5.24	27 (26.2%)	36 (80.0%)	
≤ 5.24	76 (73.8%)	9 (20.0%)	
Lymphocytes (× 10^9/L)			0.038*
> 1.435	58 (56.3%)	17 (37.8%)	
≤ 1.435	45 (43.7%)	28 (62.2%)	
Platelets (× 10^9/L)			0.016*
> 181.5	64 (62.1%)	37 (82.2%)	
≤ 181.5	39 (37.9%)	8 (17.8%)	
Monocytes (× 10^9/L)			0.001*
> 0.425	59 (57.3%)	38 (84.4%)	
≤ 0.425	44 (42.7%)	7 (15.6%)	
Hemoglobin (g/L)			0.001*
> 126.5	48 (46.6%)	8 (17.8%)	
≤ 126.5	55 (53.4%)	37 (82.2%)	
Globulin (g/L)			0.085
> 35.55	17 (16.5%)	13 (28.9%)	
≤ 35.55	86 (83.5%)	32 (71.1%)	
CRP (mg/L)			< 0.001*
CRP > 10	21 (20.4%)	45 (100.0%)	
CRP ≤ 10	82 (79.6%)	0 (0%)	
Alb (g/L)			< 0.001*
Alb < 35	42 (40.8%)	39 (86.7%)	
Alb ≥ 35	61 (59.2%)	6 (13.3%)	

*Significant differences between patients with CRP/Alb ≤ 0.6712 and CRP/Alb > 0.6712. Abbreviations: CRP, C-reactive protein; Alb, albumin; CRP/Alb, C-reactive protein/albumin ratio. The cut-off values for age; neutrophil, lymphocyte, platelet, and monocyte counts; and hemoglobin, globulin, CRP, and Alb were determined as described in the section on statistical analysis.

tests. Survival outcomes were determined by the Kaplan-Meier method, and differences were compared with log-rank test. Cox regression was used for univariate and multivariate analysis, with hazard ratio (HR) and 95% confidence interval (CI) computed using a Cox proportional hazards model. Variables significantly prognostic on univariate analysis were selected for multivariable analysis using the forward stepwise method. All statistical analyses were performed with SPSS 16.0 software (SPSS Inc., Chicago, IL USA). A two tailed *P* value < 0.05 was considered statistically significant.

The discriminatory abilities of the inflammation-based prognostic scores were evaluated by generating receiver operating characteristics (ROC) curves, by measuring and the areas under the curve (AUC). Differences in AUC were compared using MedCalc software (Version 11.4. 2.0).

Results

Table 1 shows the relationship between CRP/Alb ratio and patient demographic and clinical characteristics. An elevated CRP/Alb ratio was significantly associated with greater age (P = 0.035); higher neutrophil (P < 0.001) platelet (P = 0.016), and monocyte (P = 0.001) counts; elevated CRP (P < 0.001); and lower lymphocyte counts (P = 0.038) and hemoglobin (P = 0.001) and Alb (P < 0.001) concentrations.

ROC analysis showed that the optimal CRP/Alb cutoff for OS was 0.6712, which had a sensitivity of 38.5% and a specificity of 92.3%. Of the 148 patients, 103 (69.6%) had a CRP/Alb ratio ≤ 0.6712 and 45 (30.4%) had a CRP/Alb ratio > 0.6712. The optimal cutoff values for all other variables, as determined by ROC analysis, are shown in **Table 1**.

The 148 patients with pathologically confirmed metastatic colorectal cancer included 97

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

Characteristics	No. (%)	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Sex		0.944	0.638-1.397	0.774	0.750	0.478-1.177	0.211[a]
Male	97 (65.5)						
Female	51 (34.5)						
Age (yr)		0.764	0.499-1.169	0.215	1.052	0.660-1.678	0.830[a]
> 69.5	36 (24.3)						
≤ 69.5	112 (75.7)						
Location of primary tumor		1.059	0.700-1.602	0.787	0.864	0.559-1.336	0.510[a]
Colon	104 (70.3)						
Rectum	44 (29.7)						
Metastasis number		1.632	1.104-2.411	0.014*	1.781	1.158-2.740	0.009[a,*]
1							
≥ 2							
Hemoglobin (g/L)		1.505	1.003-2.258	0.049*	1.352	0.854-2.142	0.198[a]
> 126.5	56 (37.8)						
≤ 126.5	92 (62.2)						
Globulin (g/L)		1.166	0.710-1.914	0.544	1.316	0.787-2.199	0.295[a]
> 35.55	30 (20.3)						
≤ 35.55	118 (79.7)						
CRP/Alb		2.256	1.531-3.324	< 0.001*	2.243	1.450-3.470	< 0.001[b,*]
≤ 0.6712	103 (69.6)						
> 0.6712	45 (30.4)						
GPS		1.624	1.305-2.021	< 0.001*	1.594	1.278-1.989	< 0.001[b,*]
GPS = 0	54 (36.5)						
GPS = 1	41 (27.7)						
GPS = 2	53 (35.8)						
mGPS		1.519	1.246-1.852	< 0.001*	1.504	1.232-1.835	< 0.001[b,*]
mGPS = 0	82 (55.4)						
mGPS = 1	13 (8.8)						
mGPS = 2	53 (35.8)						
NLR		0.446	0.305-0.652	< 0.001*	0.445	0.305-0.651	< 0.001[b,*]
> 3.512	63 (42.6)						
≤ 3.512	85 (57.4)						
PLR		0.612	0.419-0.892	0.011*	0.634	0.434-0.926	0.018[b,*]
> 174.004	66 (44.6)						
≤ 174.004	82 (55.4)						
MLR		0.473	0.311-0.719	< 0.001*	0.468	0.308-0.711	< 0.001[b,*]
> 0.2729	90 (60.8)						
≤ 0.2729	58 (39.2)						

*Statistically significant. Abbreviations: HR, hazard ratio; CI, confidence interval; CRP/Alb, C-reactive protein/albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio. The cut-off values for age; neutrophil, lymphocyte, platelet, and monocyte counts; and hemoglobin, globulin, CRP, and Alb were determined as described in the section on statistical analysis. [a]Multivariate model including sex, age, primary tumor location, number of metastases, hemoglobin concentration, and globulin concentration. [b]Multivariate model including sex, age, primary tumor location, number of metastases, hemoglobin concentration, globulin concentration, and the systemic inflammation scores CRP/Alb, GPS, mGPS, NLR, PLR and MLR. The systemic inflammation scores were placed in the multivariate analysis model, respectively.

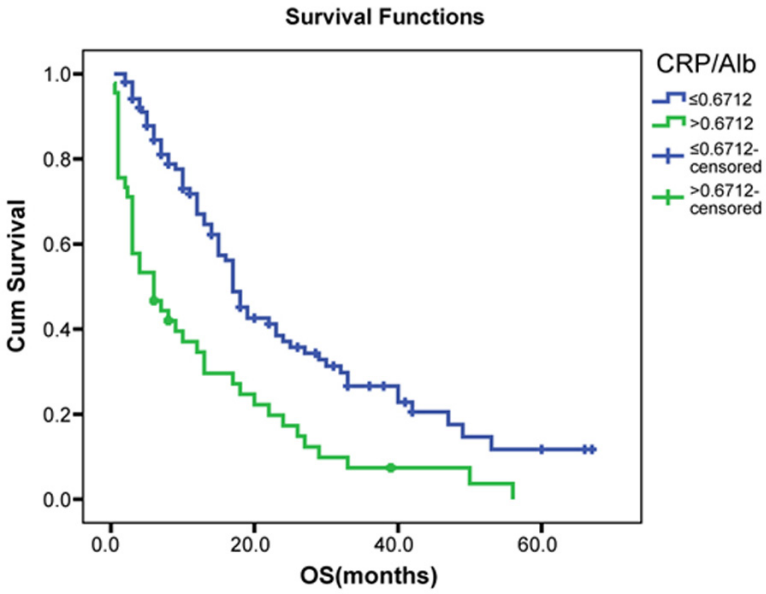

Figure 1. Kaplan-Meier analysis of overall survival (OS) in patients with CRP/Alb ratio ≤ 0.6712 and > 0.6712. OS was significantly longer in patients with CRP/Alb ratio ≤ 0.6712 than > 0.6712 (P < 0.001).

(65.5%) males and 51 (34.5%) females, of mean age 60.2 years (range, 20-74 years). Primary tumors were located in the colon in 104 (70.3%) patients and in the rectum in 44 (29.7%). All patients had stage IV disease, with 90 (60.8%) having only one metastasis number, and 58 (39.2%) having two or more. The median follow-up period was 12.0 months (range, 0.4-67.0 months). At last follow-up, 39 (26.4%) were alive and 109 (73.6%) had died (**Table 2**).

The 3-, 6-, and 9-month OS rates in patients with a CRP/Alb ratio ≤ 0.6712 were 94.0%, 91.7%, and 77.6%, respectively, whereas the 3-, 6-, and 9- month OS rates in patients with a CRP/Alb ratio > 0.6712 were 57.8%, 44.5%, and 39.5%, respectively. Median OS in patients with CRP/Alb ratios of ≤ 0.6712 and > 0.6712 group were 17.0 months (95% CI, 14.655-19.345 months) and 6.0 months (95% CI, 1.663-10.337 months), a difference that was statistically significant (P < 0.001; **Figure 1**).

Factors prognostic for OS were identified by univariate and multivariate analyses (**Table 2**). Factors prognostic on univariate analysis included number of metastases, hemoglobin concentration, CRP/Alb ratio, GPS, mGPS, NLR, PLR, and MLR. Inclusion of these variables in forward stepwise multivariate analysis showed that seven indices were independently prognostic for OS, including number of metastases (HR = 1.781, P = 0.009), GPS (HR = 1.594, P < 0.001), mGPS (HR = 1.504, P < 0.001), NLR (HR = 0.445, P < 0.001), PLR (HR = 0.634, P = 0.018), MLR (HR = 0.468, P < 0.001), and CRP/Alb (HR = 2.243, P < 0.001).

The discriminatory ability of CRP/Alb ratio was compared with that of other inflammation-based prognostic indexes by generating ROC curves for survival status at different follow-up times and statistically compared the differences in estimated AUC (**Figure 2**; **Table 3**). AUCs at 6 and 12 months for CRP/Alb ratio were 0.827 and 0.744, respectively. At both 6 and 12 months, the AUCs of the CRP/Alb ratio were significantly higher than the AUCs of GPS, mGPS, NLR, PLR and MLR. **Table 3** shows comparisons of CRP/Alb ratio with these other indices at 6 and 12 months.

Sorting of the 148 patients by GPS showed that 54 (36.5%), 41 (27.7%), and 53 (35.8%) had GPS scores of 0, 1, and 2, respectively. The 6 month survival rates in these groups were 95%, 77%, and 45.3%, respectively. GPS showed a significant association with CRP/Alb ratio (P < 0.001). Interestingly, all patients with GPS scores of 0 had CRP/Alb ratios ≤ 0.6712 (**Table 4**).

As follow-up time increased, all the inflammation-based scores showed reduced discriminatory ability, with none of these indices showing discriminatory ability at 18, 24, and 36 months (data not shown).

Discussion

Systemic inflammatory responses play an important role in carcinogenesis and tumor progression [28, 29]. Inflammatory factors derive not only from systemic reaction to malignancies, but by the secretion of acute phase proteins such as CRP [30, 31], chemokines [32], cytokines such as IL-6 [33], and circulating and infiltrating immune system cells [34].

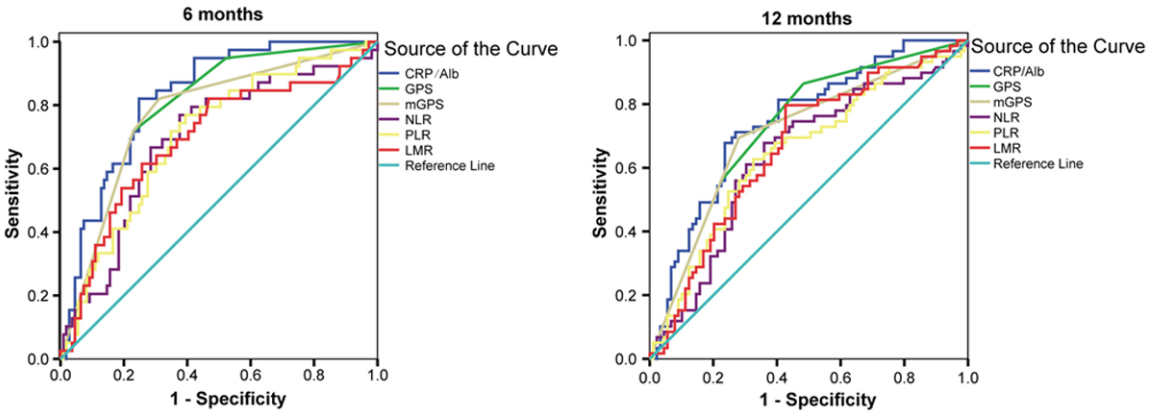

Figure 2. Receiver operating characteristic (ROC) curves at 6 and 12 months of inflammation-based prognostic indices, including the CRP/Alb ratio (continuous), GPS (categorical), mGPS (categorical), NLR (continuous), PLR (continuous) and MLR (continuous). Abbreviations: CRP/Alb, C-reactive protein/albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

Table 3. Discriminatory ability of prognostic scores, as shown by AUCs at 6 and 12 months relative to CRP/Alb

Duration of follow-up	AUC	95% CI	*P* value	Significance of comparison §*P*' value
6 months				
CRP/Alb (continuous)	0.827	0.759-0.895	< 0.001*	-
GPS	0.792	0.715-0.869	< 0.001*	P' = 0.1336
mGPS	0.772	0.686-0.859	< 0.001*	P' = 0.0230*
NLR (continuous)	0.692	0.594-0.790	< 0.001*	P' = 0.0061*
PLR (continuous)	0.704	0.611-0.796	< 0.001*	P' = 0.0126*
MLR (continuous)	0.693	0.592-0.795	< 0.001*	P' = 0.0054*
12 months				
CRP/Alb (continuous)	0.744	0.664-0.824	< 0.001*	-
GPS	0.729	0.646-0.811	< 0.001*	P' = 0.5439
mGPS	0.707	0.621-0.794	< 0.001*	P' = 0.0851
NLR (continuous)	0.639	0.546-0.731	0.004*	P' = 0.0253*
PLR (continuous)	0.649	0.558-0.741	0.002*	P' = 0.0662
MLR (continuous)	0.663	0.574-0.752	0.001*	P' = 0.0775

*Statistically significant. Abbreviations: ROC, receiver operating characteristics; AUC,area under the curve; CI, confidence interval; CRP/Alb, C-reactive protein/albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio. §Comparisons of AUC values between CRP/Alb ratio and other inflammation-based prognostic factors using z tests.

By secreting proinflammatory cytokines and formatting an inflammatory microenvironment, inflammatory cells become powerful tumor promoters [35, 36].

Elevated CRP levels have been reported to predict poor prognosis in many types of malignancy [37-40]. Elevated CRP in patients with colorectal cancer has also been reported to correlate with lower lymphocyte percentage in peripheral blood and reduced local CD4 + T-lymphocyte infiltration of tumors [41, 42]. These findings suggested that elevated CRP is involved in the linkage between decreased immunity and carcinogenesis. In addition, low serum Alb concentrations, which are indicative of malnutrition, have been with survival outcomes in patients with gastrointestinal, colorectal, lung, and ovarian cancers [43-46].

Elevations in CRP/Alb ratio, due to elevated serum CRP concentrations and/or hypoalbuminemia, may be predictive of outcomes in patients with malignancy. For example, CRP/Alb ratio was recently shown to be an independent prognostic marker in patients with hepatocellular carcinoma, comparable to that of mGPS and superior to NLR [22].

This study was designed to determine whether CRP/Alb ratio is a predictor of prognosis in patients with stage IV colorectal cancer before

Table 4. Correlation of CRP/Alb ratio with GPS

Characteristic	No. of Patients (%)		*P* value
	CRP/Alb ≤ 0.6712	CRP/Alb > 0.6712	
GPS			< 0.001*
GPS = 0	54	0	
GPS = 1	35	6	
GPS = 2	14	39	

*Statistically significant difference between patients with CRP/Alb ratio ≤ 0.6712 and > 0.6712. Abbreviation: CRP/Alb, C-reactive protein/albumin ratio; GPS, Glasgow Prognostic Score.

chemotherapy. To our knowledge, this study is the first to show that CRP/Alb ratio was superior to other inflammation-based prognostic scores in predicting 6 month survival rates in patients with metastatic colorectal cancer. Thus, CRP/Alb ratio may a promising prognostic index in metastatic colorectal cancer. The identification of patients with higher CRP/Alb ratio, and reduced overall survival, may determine which patients require more aggressive treatment schedules.

This study showed that preoperative CRP/Alb ratio may predict OS. Determining the optimal cutoff level for CRP/Alb ratio may therefore predict long-term survival [47], similar to findings for the number and type of metastases. For example, median OS was longer in patients with one (18.0 months; 95% CI: 14.191-21.809 months) than ≥ 2 (12.0 months; 95% CI: 4.006-19.994 months) metastases, and was longer in patients without (19.0 months; 95% CI 12.429-25.571) than with (13.0 months; 95% CI: 9.788-16.212 months) liver metastases.

Epidemiological and clinical studies have demonstrated that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, can protect against colorectal cancer and significantly reduce its incidence [48]. Fish oil decreases CRP/Alb ratio, improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients [49]. Patients with an elevated CRP/Alb ratio may benefit from anti-inflammatory therapy or nutritional support [50-52].

This study had several limitations, including its retrospective design and inclusion of relatively few patients from a single institution. In addition, disease-free survival could not be determined, although OS was the standard indicator for cancer prognosis study. The prognostic value of the CRP/Alb ratio requires verification in prospective multicenter studies that include larger numbers of patients and more extended follow-up time.

Conclusions

This study showed that the CRP/Alb ratio was associated with important clinical characteristics in patients with metastatic colorectal cancer. Increased CRP/Alb ratios were significantly associated with poorer survival and very low CRP/Alb ratio levels are with excellent survival. CRP/Alb ratios at 6 and 12 months had higher AUC values than markers of systemic inflammation, including GPS, mGPS, NLR, PLR and MLR, and was superior in predicting 6 month OS. Identifying patients with higher CRP/Alb ratio may enable more aggressive treatment schedules. The CRP/Alb ratio may be a promising inflammation-based prognostic factor for predicting 6 month survival in patients with metastatic colorectal cancer.

Disclosure of conflict of interest

None.

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