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Original Article

Prognostic significance of serum C-reactive protein to albumin ratios in esophageal cancer patients receiving radical radiotherapy

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Abstract: Background: Serum C-reactive protein to albumin (CRP/ALB) ratios have been reported to be independent prognostic factors in patients with various types of cancer, including esophageal cancer (EC). However, the prognostic value of the ratio in EC patients receiving radical radiotherapy has not yet been evaluated. Therefore, the current study performed a retrospective analysis of EC patients that underwent radical radiotherapy, aiming to assess prognostic roles of the ratio. Methods: Pretreatment blood tests were used to calculate serum CRP/ALB ratios. The optimal cut-off value of CRP/ALB ratio was determined using receiver operating characteristic curves (ROC). Chi-square (χ^2) tests were conducted to analyze the association between pretreatment serum CRP/ALB ratios and clinicopathological characteristics. Overall survival (OS) was analyzed using the Kaplan-Meier method. Differences were assessed using log-rank testing. Univariate analysis was employed to evaluate the prognostic influence of CRP/ALB ratios and other clinicopathological factors on OS. To further evaluate the independent prognostic value of CRP/ALB ratios, multivariate regression analysis was applied. Results: The optimal cut-off value for the pretreatment serum CRP/ALB ratio was 0.15. The CRP/ALB ratio was ≥ 0.15 in 66.7% (46/69). Moreover, CRP/ALB ratios showed a significant relationship with degree of tumor invasion (p = 0.029). In addition, OS rates were significantly worse in the high CRP/ALB ratio group than the low CRP/ALB ratio group (χ^2 = 8.473; p = 0.004). Similarly, OS rates were significantly worse in the high CRP/ALB ratio (χ^2 = 4.322; p = 0.038) group when patients were stratified by therapeutic approaches. Furthermore, univariate analysis showed that OS was significantly related with tumor differentiation (p = 0.04), invasion degree (p = 0.038), lymph node metastasis (p = 0.01), tumor stage (p = 0.038), elevated CRP/ALB ratio (p = 0.005), and the use of concurrent chemotherapy (p = 0.019). Finally, multivariate analysis indicated that an elevated CRP/ALB ratio was an independent prognostic factor for OS (hazard ratio 2.463; 95% confidence interval 1.183-5.126; p = 0.016). Conclusion: Present results suggest that serum CRP/ALB ratios may be independent prognostic factors, serving as biomarkers for predicting the prognosis of EC patients receiving radical radiotherapy.

Keywords: C-reactive protein, albumin, inflammation, esophageal carcinoma, radiotherapy

Introduction

Esophageal cancer (EC) is one of the most lethal human malignancies, causing over 400 thousand deaths per year [1]. Unfortunately, 70%~80% of patients with EC are discovered and diagnosed at advanced stages. This may be due to hidden early symptoms and a lack of effectively early diagnosis measures [2]. Most patients have already lost the opportunity to have surgical resections. Therefore, radiotherapy serves as a major modality for patients with locally unresectable lesions. In spite of advances in technology of radiotherapy, which include three-dimensional conformal radiation therapy (3-DCRT) and intensity-modulated radiation therapy (IMRT), the prognosis of patients with EC still remains extremely poor. This disease carries a local uncontrolled or recurrent rate of about 80% and 5-year survival rate of approximate 10% [2]. Therefore, assessment of factors related to prognosis is urgent for the administration of EC patients undergoing radiotherapy.

Growing evidence has indicated that the inflammatory microenvironment plays an important role in tumor progression, including invasion and metastasis [3-5]. Various inflammatory response biomarkers, such as C-reactive protein (CRP) and modified Glasgow prognostic scores

Table 1. Characteristics of patients undergoing radical radiotherapy

Characteristics	No. of patients (%)
Age	
< 65 years	28 (40.6%)
≥ 65 years	41 (59.4%)
Gender	
Female	9 (13.0%)
Male	60 (87.0%)
Smoking	
Never	15 (21.7%)
Ever	54 (79.3%)
Alcohol consumption	
Never	13 (18.8%)
Ever	56 (81.2%)
Tumor type	
Squamous cell carcinoma	69 (100%)
Differentiation	
Well	21 (30.4%)
Intermediate	23 (33.3%)
Poor or undifferentiated	25 (36.3%)
Tumor location	
Upper	21 (30.4%)
Middle	29 (42.0%)
Lower, GE junction	19 (27.6%)
Tumor depth	
T2	19 (27.6%)
T3	43 (62.3%)
T4	7 (10.1%)
Nodal status	
N0	33 (47.8%)
N1	29 (42.0%)
N2	7 (10.2%)
Tumor stage	
IIIII	56 (81.2%)
IV	13 (18.8%)
Squamous cell carcinoma (SCC) antigen	
≤ 1.5	32 (46.4%)
> 1.5	37 (53.6%)

(mGPS), calculated from the concentration of serum CRP and albumin (ALB), have been identified as effectively prognostic factors in multiple malignancies [6, 7]. Recently, the serum CRP/ALB ratio, a novel prognostic factor, has been reported to possess more accurate prognostic value in patients with various types of malignancies, compared to CRP alone or mGPS [8-10]. However, there have been few previous reports focusing on the prognostic value of CRP/ALB ratios concerning management of patients with EC [11].

To the best of our knowledge, there are no published studies concentrating on the prognostic significance of CRP/ALB ratios in EC patients administrated with radiotherapy. The current study applied this biomarker to EC patients, predicting and monitoring the outcomes of radiotherapy. The aim of the current study was to evaluate the prognostic significance of the CRP/ALB ratio as an independent biomarker for survival of EC patients administrated with radical radiotherapy.

Methods

Patients

The current study retrospectively reviewed medical records of patients with histologically proven esophageal squamous cell carcinoma (ESCC). These patients did not undergo surgery. Thus, they were selected for radiotherapy with a curative intent, between January 2012 and December 2015. Inclusion criteria: (1) ESCC patients without surgery; and (2) Patients undergoing radical radiotherapy with or without chemotherapy. Exclusion criteria: Distant metastases, acute infections, and chronic inflammatory diseases, such as vasculitis and rheumatosis. Finally, a total of 69 eligible patients were selected, with a mean age of 67.7 years. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores of all patients were less than or equal to 3. Most of them were males (87%). Regarding treatment options, 31 (45%) patients were treated with concurrent chemoradiotherapy. Moreover, 5-fluorouracil (5-FU) + cisplatin (DDP) was selected as the chemotherapy regimen by the same medical oncologists. It was delivered from the first to third day of weeks 1 and 4 during radiotherapy. Radiotherapy, alone, was employed for treatment of the remaining cases. IMRT technology with a fraction dose of 2 Gy was applied for all patients using a Varian linear accelerator with 6MV-X-rays. Delineation of target volumes included primary esophageal lesions and locally metastatic lymph nodes. It was consistently supervised by two experienced radiation oncologists. Tumor-node-metastasis (TNM) stages were assessed based on American Joint Committee on Cancer (AJCC) 7th edition. All patient characteristics are summarized in **Table 1**.

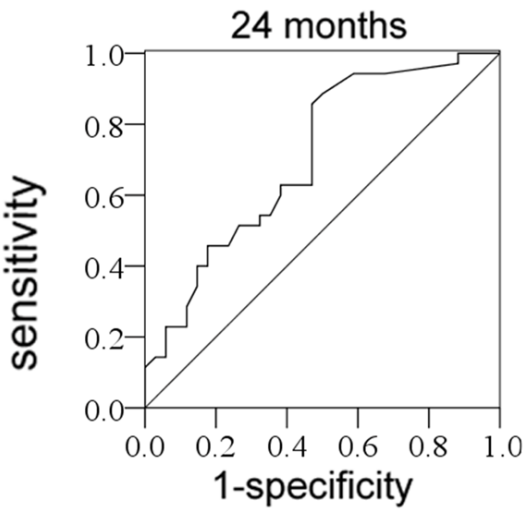

Figure 1. Receiver operating characteristic (ROC) curve analysis of the pretreatment serum CRP/ALB ratio in EC patients administrated with radical radiotherapy combined with or without chemotherapy. Area under the curve = 0.706; 95% confidence interval = 0.583-0.829; $p = 0.003$.

Evaluations

Pretreatment blood samples were collected within one week before the initiation of radiotherapy. Serum CRP and ALB concentrations were measured using a chemiluminescent immunoassay (Beckman, CA, USA), according to manufacturer protocol. Serum CRP concentrations of more than 5 mg/l or ALB concentrations lower than 35 g/l were considered to be abnormal. Pretreatment CRP/ALB ratios were calculated by dividing the serum CRP level by the serum ALB level. Overall survival (OS) was measured from the date of initiation of radiotherapy to death from any cause or last living contact. Survival data of patients was obtained either from hospital records or by telephone interviews. The patients were followed up with physical examinations and blood tests, including measurement of squamous cell carcinoma (SCC) antigens, as well as ultrasonography, esophageal radiography, and computed tomography procedures.

Statistical analysis

The optimal cut-off value for pretreatment serum CRP/ALB ratios was investigated using receiver operating characteristic (ROC) curves. The significance of correlation levels between the CRP/ALB ratio and clinicopathological characteristics was analyzed using Chi-square (χ^2) tests. Duration of OS was calculated according to the Kaplan-Meier method. Differences in survival curves were assessed using log-rank tests. Significant parameters identified by univariate analysis were evaluated using multivariate analysis, according to Cox's proportional hazard model, in which the backward stepwise method was selected. Statistical analyses were conducted using SPSS version 17.0 software package. All tests were two-sided. *P*-values < 0.05 indicate statistical significance.

Ethical consideration

This retrospective study was conformed to the provisions of the Declaration of Helsinki of 1975. The current study was approved by the Ethics Committee of Jinshan hospital affiliated Fudan university and all patients provided written informed consent.

Results

Classifications according to pretreatment serum CRP/ALB ratios

The pretreatment serum CRP/ALB ratio, a continuous variable, was used as the test variable, while 24-month survival was used as the state variable in ROC curves (**Figure 1**). The optimal cut-off value for the CRP/ALB ratio was 0.15 (sensitivity: 85.7%; specificity: 52.9%), according to Youden's index [12]. Therefore, 0.15 was set as the cut-off value. Patients with a CRP/ALB ratio ≥ 0.15 and < 0.15 were classified into high CRP/ALB ratio (n = 46) and low CRP/ALB ratio (n = 23) groups, respectively.

Correlation levels between the pretreatment serum CRP/ALB ratio and clinicopathological factors

Correlation levels between the pretreatment serum CRP/ALB ratio and clinicopathological factors are shown in **Table 2**. CRP/ALB ratios showed no significant relationship with any clinicopathological factors, except for degree of tumor invasion.

OS analysis based on the pretreatment serum CRP/ALB ratio

OS rates were significantly worse in the high pretreatment serum CRP/ALB ratio group than

Table 2. Correlation of the pretreatment serum CRP/Alb ratio with clinicopathological characteristics of EC patients administrated with radical radiotherapy combined with or without chemotherapy

Characteristics	No. of patients		*p* value
	CRP/Alb ratio < 0.15	CRP/Alb ratio ≥ 0.15	
Age			0.072
< 65 years	13	15	
≥ 65 years	10	31	
Gender			0.468
Female	4	5	
Male	19	41	
Smoking			0.550
Never	6	9	
Ever	17	37	
Alcohol consumption			1.000
Never	4	9	
Ever	19	37	
Differentiation			0.855
Well	8	13	
Intermediate	7	16	
Poor or undifferentiated	8	17	
Tumor location			0.157
Upper	8	13	
Middle	12	17	
Lower, GE junction	3	16	
Tumor depth			0.029
T2	11	8	
T3	11	32	
T4	1	6	
Nodal status			0.306
N0	15	18	
N1	10	19	
N2	2	5	
Tumor stage			0.097
IIIII	21	35	
IV	2	11	
SCC antigen			1.000
≤ 1.5	11	21	
> 1.5	12	25	

Notes: SCC; Squamous cell carcinoma.

in the low pretreatment serum CRP/ALB ratio group (χ^2 = 8.473; p = 0.004) (**Figure 2A**). Similarly, subanalysis on EC patients treated with concurrent chemoradiotherapy showed that OS rates were significantly worse in patients with a high CRP/ALB ratio (χ^2 = 4.322; p = 0.038) (**Figure 2B**).

Prognostic factors influencing overall survival

Correlation levels between OS and various clinicopathological factors are shown in **Table 3**. According to results of univariate analysis, OS showed significant relationships with tumor differentiation (p = 0.04), invasion degree (p = 0.038), lymph node metastasis (p = 0.01), tumor stage (p = 0.038), elevated CRP/ALB ratio (p = 0.005), and the use of concurrent chemotherapy (p = 0.019). Multivariate analysis indicated that lymph node metastasis (hazard ratio 1.775; 95% confidence interval 1.084-2.907; p = 0.033), tumor stage (hazard ratio 2.310; 95% confidence interval 1.142-4.675; p = 0.02), the use of concurrent chemotherapy (hazard ratio 0.501; 95% confidence interval 0.240-1.044; p = 0.031), and elevated CRP/ALB ratio (hazard ratio 2.463; 95% confidence interval 1.183-5.126; p = 0.016) were independent prognostic factors for OS.

Side effects

During therapy, two (8%) and three (6%) patients emerged with grade 3 or more hematological toxicities in low and high CRP/ALB groups, respectively. There were no significant differences between the two groups (χ^2 = 0.454; p = 0.500). Additionally, three (13%) and five (11%) patients appeared with grade 3 or more symptoms of the digestive tract in low and high CRP/ALB groups, respectively. Similarly, there were no significant differences between the two groups (χ^2 = 0.071; p = 0.790). However, there were no other grade 3 cases or more side effects in either group. Moreover, follow-up treatments were not suspended after effective intervention for these patients.

Discussion

Although improvements in clinical outcomes of patients with esophageal carcinomas have been made, prognosis remains very poor. Surgery, alone, and combined neoadjuvant radio-chemotherapy are standard treatments for early-stage and locally advanced diseases, respectively. However, non-operable administration is

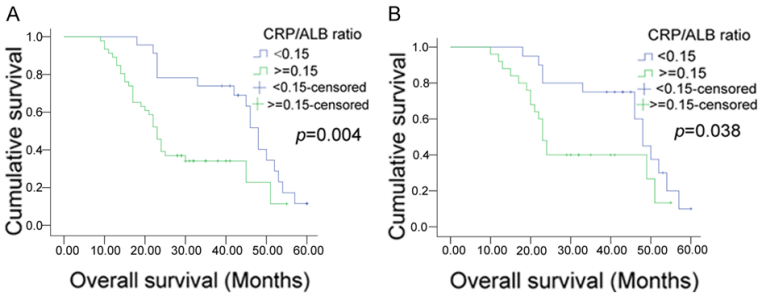

Figure 2. Kaplan-Meier curves showing the difference in OS for EC patients grouped according to the cut-off value of the pretreatment serum CRP/ALB ratio. A: OS analysis of all patients; B: OS sub-analysis of patients administrated with concurrent radiochemotherapy.

also an importantly therapeutic strategy for patients with unresectable diseases in clinical practice [13]. The present study retrospectively analyzed clinical data from patients with esophageal carcinomas that were intolerant to surgery or chemotherapy due to poor performance status or age reasons, Complete resections were, therefore, technically unfeasible. The patients finally underwent potentially definitive radiotherapy procedures, combined with or without synchronous chemotherapy. This decision is always made by a multidisciplinary team, involving radiation and medical oncologists, dedicated surgeons, and radiologists. Results revealed that elevated CRP/ALB ratios prior to radiotherapy are independent predictable factors for overall prognosis of patients receiving a radiation dose of > 50 Gy, as recommended by Radiation Therapy Oncology Group (RTOG) in the RTOG8501 study [14]. Consistent with previous studies, several factors were associated with worse survival of patients with esophageal carcinomas, including more advanced tumor stage and whether concomitant chemotherapy was employed [14, 15].

Conventional clinicopathological characteristics, including tumor stage and circumferential resection margin, have been considered pivotal in determining the prognosis of patients with cancer. However, it is now clear that the survival of patients is not solely determined by malignancy pathology. Indeed, there have been multiple studies concerning the close relationship between the inflammatory microenvironment and survival rates of patients with malignant carcinomas, such as colorectal and prostate cancer, since the relationship was first disclosed by Virchow in 1863 [16-18]. Studies reported by Katz et al. demonstrated that non-cellular components in the inflammatory microenvironment, such as tumor growth factor-β (TGF-β), signal transducers, and activators of transcription 3 (STAT3), play an important role in tumor proliferation, differentiation, invasion, and metastasis, as well as in resistance to radiotherapy [19-22]. Moreover, TGF-β may prevent deoxyribonucleic acid (DNA) from damage induced by gamma rays, reduce cell apoptosis, and enhance cell viability [23]. In addition, the inflammatory microenvironment could also result in local lesion hypoxia, closely related to resistance of tumor cells to radiotherapy. However, the complex interaction between inflammatory cascades and cancer progression is not well understood. More research is necessary.

C-reactive protein (CRP), one of the most important inflammatory markers, has been shown to mediate interactions between cancer and its inflammatory microenvironment. CRP has been considered useful in predicting therapeutic outcomes in patients with malignancies [24, 25]. Elevated CRP levels contribute to tumor invasion and metastasis via activating extracellular signal-regulated kinases to induce the transcriptional activation of matrix metaloproetinase-9 (MMP-9) [26]. Similarly, concentrations of serum albumin, which reflect the nutritional status of patients, have been widely recognized to be an independent prognostic factor for various types of malignancies [27]. Combining the serum CRP with albumin values, the CRP/ALB ratio is now considered to be a more accurate marker. A study reported by Shibutani et al. showed that the CRP/ALB ratio was more closely correlated with survival than CRP values alone, showing outstanding prognostic value, compared to other inflammation-based prognostic markers [8]. In the present study, the CRP/ALB ratio was similarly shown to be a valuable marker for prediction of survival of EC patients treated with radical radiotherapy. Indeed, the current study is not the first to evaluate the association between the CRP/ALB ratio and outcomes of patients with EC.

Table 3. Univariate and multivariate analysis of correlation levels between OS and various clinico-pathological factors

Characteristics	Case (n)	Univariate analysis			Multivariate analysis		
		Mean (95% CI)	Median	*p* value	Hazard ratio	95% CI	*p* value
Age							
< 65 years	28	37.0 (30.8-43.2)	45	0.25			
≥ 65 years	41	31.9 (26.5-37.5)	23				
Gender							
Female	9	33.6 (20.9-46.3)	33	0.83			
Male	60	34.3 (29.8-38.7)	24				
Smoking							
Never	15	41.8 (33.2-50.5)	48	0.06			
Ever	54	31.9 (27.4-36.4)	23				
Alcohol consumption							
Never	13	40.1 (30.7-49.5)	48	0.13			
Ever	56	32.5 (28.1-37.0)	23				
Differentiation					1.271	0.864-1.869	0.223
Well	21	40.9 (32.9-48.8)	48	0.04			
Intermediate	23	33.4 (25.9-40.9)	24				
Poor	25	29.8 (23.7-35.9)	23				
Tumor location					0.848	0.570-1.259	0.413
Upper	21	32.5 (24.9-39.9)	23	0.65			
Middle	29	34.1 (27.6-40.6)	24				
Lower	19	35.4 (27.9-42.7)	42				
pT status					1.359	0.875-2.433	0.147
T2	19	42.1 (34.3-49.9)	48	0.038			
T3	43	32.7 (27.5-37.9)	24				
T4	7	25.4 (12.7-38.1)	21				
pN status					1.775	1.084-2.907	0.033
N0	33	38.3 (32.1-44.4)	46	0.01			
N1	29	32.8 (26.5-39.1)	24				
N2	7	21.3 (12.5-30.1)	18				
Tumor stage					2.310	1.142-4.675	0.020
II-III	56	36.1 (31.4-40.9)	42	0.038			
IV	13	26.8 (18.7-34.9)	22				
CRP/ALB ratio					2.463	1.183-5.126	0.016
< 0.15	23	43.8 (38.4-49.3)	48	0.005			
≥ 0.15	46	29.4 (24.5-34.3)	22				
Treatment					0.501	0.240-1.044	0.031
Radiotherapy	23	28.4 (20.2-36.6)	22	0.019			
RCT	46	36.9 (32.2-41.7)	46				
SCC antigen					0.91	0.474-1.751	0.778
< 1.5	31	35.9 (30.4-41.4)	42	0.424			
≥ 1.5	38	31.7 (25.5-37.9)	23				

Notes: RCT: Radio-and chemotherapy; SCC: squamous cell carcinoma; CRP/ALB: C-reactive protein/albumin.

Previous studies have also shown the ratio to be an independent predictor of survival in patients with operable EC [11, 28].

In the present study, 0.15 was set as the optimal cut-off value of the CRP/ALB ratio. This was based on the results of ROC analysis. However,

different cut-off values have been used in various published studies on EC patients. Inflammatory markers have been shown to be related with the degree of disease progression, such as tumor invasion range and lymph node status. Therefore, appropriate cut-off values may be aberrant between different studies, according to primary characteristics of the patients.

Several limitations existed in the present study, however. First, a relatively small number of patients were reviewed. The follow-up time was not very long. Second, some patients did not receive concurrent chemoradiotherapy, which has been recommended as a standard regimen for non-operable patients based on the RTOG8501 study. Intolerance to chemotherapy is a major reason of avoiding chemoradiotherapy. Therefore, a prospective study with a larger number of patients should be performed, confirming present findings.

Conclusion

In summary, present preliminary data indicates that the pretreatment serum CRP/Alb ratio is a potential inflammation-based prognostic factor in EC patients administrated with radical radiotherapy. However, further investigations are warranted to clarify the mechanisms explaining the observed association between elevated CRP/ALB ratio and poor outcomes.

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Disclosure of conflict of interest

None.

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