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ORIGINAL RESEARCH

Prognostic value of the C-reactive protein/albumin ratio in patients with laryngeal squamous cell carcinoma

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Purpose: The present study was designed to retrospectively evaluate the prognostic value of the C-reactive protein/albumin (CRP/ALB) ratio in laryngeal squamous cell carcinoma (LSCC).

Methods: One hundred and twenty-nine newly diagnosed LSCC patients admitted between May 2006 and October 2011 were retrospectively reviewed. Their serum CRP and ALB were quantified preoperatively. The relationship between the CRP/ALB ratio and the clinicopathologic features was analyzed. Receiver operating characteristic curve was used to calculate the prognostic value of the CRP/ALB ratio. Then, the Cox proportional hazards model was used in univariate and multivariate analyses to identify significant prognostic factors associated with disease-free survival and overall survival.

Results: The cutoff value for CRP/ALB ratio was 0.047. An elevated CRP/ALB ratio was significantly associated with nodal metastasis, late disease stage, and recurrence. Also, high values of CRP/ALB ratio were significant predictors for poor overall survival and disease-free survival on multivariate analysis.

Conclusion: Pretreatment CRP/ALB ratio may be a significant prognostic marker in LSCC.

Keywords: C-reactive protein/albumin ratio, laryngeal squamous cell carcinoma, prognosis, survival

Introduction

Laryngeal squamous cell carcinoma (LSCC) can commonly be found among head and neck squamous cell carcinomas, and comprises 1%–2% of all malignancies.[1] The underlying mechanism of laryngeal carcinogenesis is still uncertain, and reliable diagnostic and prognostic value markers are still insufficient. Few studies have reported that the systemic inflammation plays a significant role in the progression and prognosis of many cancers.[2] Also, several inflammation-based prognostic scores, including neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), have been reported to have prognostic significance in LSCC.[3–6]

Now, a novel inflammation-based prognostic index, the C-reactive protein/albumin (CRP/ALB) ratio, has been shown to be an independent prognostic marker, and compared with other inflammation-based prognostic markers, it has significant prognostic value in esophageal cancer, nasopharyngeal cancer, and hepatocellular carcinoma.[7–9] However, the prognostic significance of the CRP/ALB ratio has not been evaluated in patients with LSCC yet. Hence, we performed a study retrospectively to assess its prognostic value in LSCC patients.

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Materials and methods
Patients

We retrospectively reviewed 129 patients with newly diagnosed LSCC admitted between May 2006 and October 2011 from the Department of Otolaryngology, Head and Neck Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University. This study was carried out after ethical approval was granted by the Ethics Committee of Sun Yat-sen Memorial Hospital. All patients gave their written informed consent to review their medical records and for this study. Patients with synchronous cancer, history of cancer, presence of infection or inflammatory conditions, immune disease, and those without pretreatment blood test were excluded from current study. Also, patients who received neoadjuvant radiotherapy or chemotherapy were also excluded from the study. All blood tests were retrieved before the patients received any form of treatment. Quantification of CRP and ALB in serum was undertaken at the laboratories of Sun Yat-sen Memorial Hospital through a standard methodology. All the medical records of the patients as well as their clinical information were reviewed and collected (including age at diagnosis, sex, tumor-node-metastasis [TNM] classification, treatment modalities, pretreatment serum CRP and ALB concentrations, time to recurrence, and death). The CRP/ALB ratio was calculated as serum CRP divided by serum ALB level.[7–9] Then, all patients received standard surgery (and radio/chemotherapy, if applicable) according to the National Comprehensive Cancer Network guidelines. Patients with adverse features (eg, extracapsular node spread, positive margins, pT4 primary, N2 or N3 nodal disease, vascular embolism, and perineural invasion) had postoperative radiotherapy or chemoradiotherapy. All patients were followed up for at least 5 years or until October 2016 or until their death.

Statistical analysis

Tumor clinical staging was performed according to the seventh edition of the American Joint Committee on Cancer staging system. Then they were categorized into two subgroups: early stage (stages I and II) and late stage (stages III and IV).

Comparison between the groups was performed using the Mann–Whitney U-test (for normal distribution data) and Student's t-test (for normal data) for continuous variables and the Chi-square test for categorical variables.

Receiver operating characteristic (ROC) curves were plotted to generate the optimal cutoff point for overall survival (OS). Survival curves were analyzed according to the Kaplan–Meier method and compared with the log-rank test to evaluate the differences between survival rates among different groups. Multivariable analysis using a Cox proportional hazards model was performed to find the prognostic factors associated with OS and disease-free survival (DFS) based on those factors that proved to be significant in the univariate analysis. A two-tailed P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS v22.0 (IBM Corporation, Armonk, NY, USA).

Results
Patient characteristics

A total of 129 patients were enrolled in this study, in which males were predominant (92.2%). The median age of these patients was 61 (range: 29–82) years. According to the seventh edition of the American Joint Committee on Cancer TNM staging system, 42 (32.6%) patients were classified as stage I, 38 (29.5%) as stage II, 32 (24.8%) as stage III, and 17 (13.2%) as stage IV. Eighty-five (65.89%) patients underwent surgery alone and 44 (34.41%) underwent surgery with radiotherapy or radiochemotherapy postoperatively.

The median of CRP value was 5.214 mg/L (range: 0.232–69.285) and that of ALB value was 40.100 g/L (range: 30.900–47.900). The median CRP/ALB ratio was 0.374 (range: 0.006–2.020). ROC curves were plotted based on OS, and the area under the curve was used to determine the discriminative ability of the CRP/ALB ratio (Figure 1).
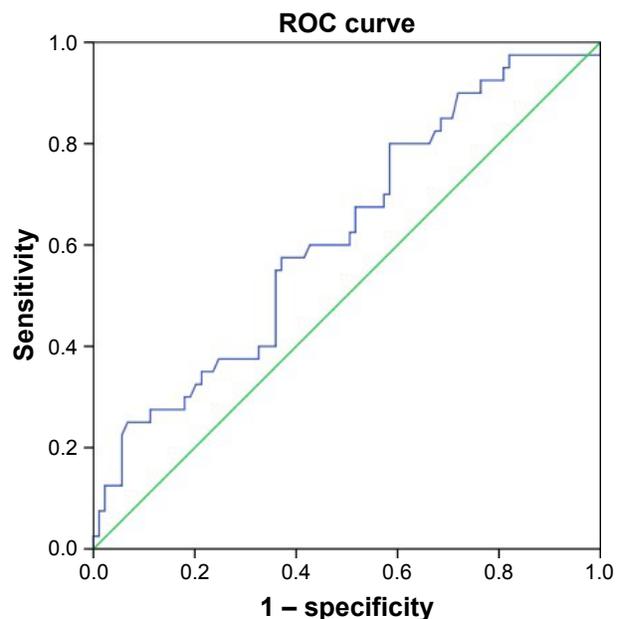
Figure 1 ROC curve analysis of the CRP/ALB ratio for survival status among the 129 patients with LSCC.
Notes: The optimal cutoff value was 0.047 according to the ROC analysis (area 0.62 [95% CI, 0.52–0.72], $P<0.05$). Diagonal segments are produced by ties. Green line represents reference line. Blue line represents the curve for CRP/ALB ratio.
Abbreviations: CI, confidence interval; CRP/ALB, C-reactive protein/albumin; LSCC, laryngeal squamous cell carcinoma; ROC, receiver operating characteristic.

Table 1 Patient demographics and clinical characteristics

Characteristics	Total n, (%)	CRP/ALB ratio		P-value
		<0.047 n, (%)	≥0.047 n, (%)	
Total	129	73	56	
Age, years				0.53
≤60	64 (49.6)	38 (52.1)	26 (46.4)	
>60	65 (50.4)	35 (47.9)	30 (53.6)	
Sex				0.30
Male	119 (92.2)	66 (90.4)	53 (94.6)	
Female	10 (7.8)	7 (9.6)	3 (5.4)	
Smoking status				0.96
Nonsmokers or ex-smokers	51 (39.6)	29 (39.7)	22 (39.2)	
Smokers	78 (60.4)	44 (60.3)	34 (60.8)	
Nodal classification				<0.01
N0	87 (67.4)	57 (78.1)	30 (53.6)	
N+	42 (32.6)	16 (21.9)	26 (46.4)	
Disease stage				<0.05
I/II	80 (62.0)	51 (69.9)	29 (51.8)	
III/IV	49 (38.0)	22 (30.1)	27 (48.2)	
Recurrence				<0.05
Yes	46 (35.6)	20 (27.4)	27 (48.2)	
No	83 (64.4)	53 (72.6)	29 (51.8)	

Abbreviation: CRP/ALB, C-reactive protein/albumin.

The optimal CRP/ALB ratio cutoff value for OS was 0.047, and the patients were divided into two subgroups based on this cutoff value (<0.047, n=73; ≥0.047, n=56).

Table 1 shows the associations between CRP/ALB ratio and clinicopathologic characteristics. A higher CRP/ALB ratio was shown to have association with nodal metastasis ($P<0.01$), a late disease stage ($P<0.05$), and cancer recurrence ($P<0.05$). No significance in this ratio was observed for any of the other characteristics.

Survival analysis

During a median of 77 (interquartile range [66–94]) months' follow-up, a total of 40 (31%) and 44 (34.1%) experienced death or recurrence of LSCC, respectively. In patients with CRP/ALB ratio <0.047, the median OS was 88 months and the interquartile (P25, P75) was 68 and 97 months, respectively. In patients with CRP/ALB ratio ≥0.047, the median OS was 73 months and the interquartile (P25, P75) was 61 and 89 months, respectively. For the entire cohort, the 5-year OS and DFS were 69% and 50.4%, respectively.

In Table 2, univariate analysis reveals that the nodal metastasis ($P<0.01$), late disease stage ($P<0.01$), and higher CRP/ALB ratio ($P=0.01$) had a significant association with OS. The 5-year OS rate was significantly better in patients with CRP/ALB ratio <0.047 (Figure 2). For DFS also, it revealed the same outcome (nodal metastasis [$P<0.01$]; late disease stage [$P<0.01$]; higher CRP/ALB ratio [$P<0.01$]).

Variables with significance in univariate analysis were involved in multivariate analysis to identify independent prognostic factors for OS and DFS, respectively (Table 3). Multivariate analysis suggested that nodal metastasis (hazard ratio [HR] =2.56; 95% confidence interval [CI] =1.12–5.87; $P<0.05$), late disease stage (HR [95% CI] =3.20 [1.36–7.48], $P<0.01$), and higher CRP/ALB ratio (HR [95% CI] =2.56

Table 2 Univariate Cox regression analysis for OS and DFS in patients with laryngeal squamous cell carcinoma

Variables	No of patients	OS			DFS		
		No of events	HR (95% CI)	P-value	No of events	HR (95% CI)	P-value
Sex				0.11			0.08
Male	119	39			43		
Female	10	1	0.20 (0.03–1.47)		1	0.18 (0.02–1.28)	
Age, years				0.26			0.97
≤60	64	23			22		
>60	65	17	0.70 (0.37–1.31)		22	0.97 (0.54–1.75)	
Smoking				0.78			0.67
Nonsmoker or ex-smoker	51	19			20		
Smoker	78	21	1.23 (0.67–1.99)		24	1.06 (0.56–1.76)	
Nodal classification				<0.01			<0.01
N0	87	14			22		
N+	42	26	4.58 (2.42–8.61)		20	2.43 (1.33–4.45)	
Disease stage				<0.01			<0.01
I/II	80	12			19	4.68 (2.49–8.81)	
III/IV	49	28	5.94 (2.99–11.78)		25		
CRP/ALB ratio				<0.05			<0.01
<0.047	73	17			18		
≥0.047	56	23	2.13 (1.15–3.93)		26	2.36 (1.28–4.36)	

Abbreviations: CRP/ALB, C-reactive protein/albumin; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.
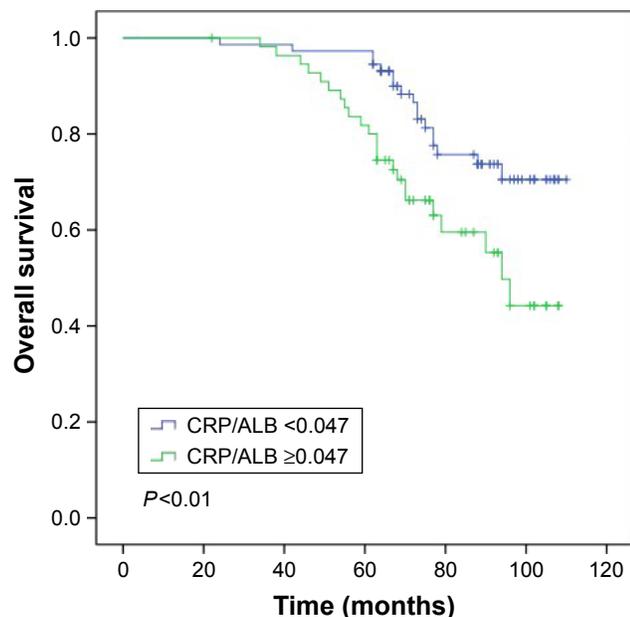
Figure 2 Overall survival curves for the 129 patients with LSCC stratified by the CRP/ALB ratio (P<0.01).
Abbreviations: CRP/ALB, C-reactive protein/albumin; LSCC, laryngeal squamous cell carcinoma.

[1.09–5.86], *P*<0.05) were the independent indicators affecting OS. However, in DFS, only late disease stage (HR [95% CI] =2.91 [1.40–6.07], *P*<0.01) and higher CRP/ALB ratio (HR [95% CI] =1.97 [1.12–4.06], *P*=0.02) were the independent indicators affecting DFS.

Discussion

The CRP/ALB ratio in this study was an independent prognostic factor for OS and DFS in the LSCC patients. To the best of our knowledge, this is the first study that evaluates the prognostic value of the CRP/ALB ratio in LSCC patients.

Several studies revealed the significant role of systemic inflammation in the prognosis of patients.[10] In the tumor microenvironment, inflammatory cytokines produced by cancer cells can promote inflammation[11] and chemokines may promote cancer metastasis.[12] Some parameters, including NLR and PLR, have been reported for their significance in assessing the systemic inflammatory response.[3,5,13] Tu et al[3] and Fu et al[14] reported that preoperative NLR was associated with recurrence and poor OS. Also, Wang et al reported PLR to be an independent predictor for poor OS and relapse-free survival.[13]

Recently, an increasing number of studies exploring the relationship between CRP/ALB ratio and several cancers have been conducted, including liver, lung, gastric, and esophageal cancers.[7–9,15,16] Besides, Ranzani et al revealed that the CRP/ALB ratio had a more precise prognosis value than CRP level alone to predict 90-day mortality in sepsis patients.[17] In the current study, the CRP/ALB ratio had a significant connection with OS and DFS; the CRP/ALB cutoff value was 0.047 and had an interactive role in systemic inflammatory responses and dystrophia.[9] However, the underlying mechanisms by which the CRP/ALB ratio regulates the survival of cancer patients are still uncertain. To start with, an elevated CRP level may have a connection with the existence of a systemic inflammatory response.[9] Also, tumor cell necrosis and invasion could positively upregulate an inflammatory response.[18] Marsik et al retrospectively analyzed a large cohort of patients and reported that there were nearly 30% in 10 years all-cause mortality exhibited a higher CRP level (>80 mg/L) and that a highly increased CRP level had a connection with higher mortality due to cancer and noncancer all-cause vascular diseases.[10] Furthermore, laryngeal carcinoma was found to generate interleukin-6, which could induce liver to synthesize more CRP and reduce the levels of ALB synthesized by hepatic cells,[19,20] and play a role as an autocrine growth factor, so as to enhance the proliferation of cancer cells.[21]

Table 3 Multivariate Cox regression analysis for OS and DFS in patients with laryngeal squamous cell carcinoma

Variables	No of patients	OS		DFS	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Nodal classification			<0.05		0.72
N0	87				
N+	42	2.56 (1.12–5.87)		1.15 (0.545–2.41)	
Disease stage			<0.01		<0.01
I/II	80				
III/IV	49	3.20 (1.36–7.48)		2.91 (1.40–6.07)	
CRP/ALB ratio			<0.05		<0.05
<0.047	73	2.56 (1.09–5.86)		1.97 (1.12–4.06)	
≥0.047	56				

Abbreviations: CRP/ALB, C-reactive protein/albumin; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Our current finding may suggest that LSCC patients with an increased CRP/ALB ratio may need a more frequent follow-up. Also, they may benefit from anti-inflammatory and nutritional support therapy.[22,23] Indeed, the relationship between nutrition and inflammation had been confirmed by many researches, and systemic inflammatory response was found to lead to a worse nutritional status and, subsequently, a poor prognosis in cancer patients.[24–26] Furthermore, several studies had revealed that cancer patients could benefit from ω-3 polyunsaturated fatty acids in fish oil as it could improve their CRP/ALB status, immune function, as well as prevent weight loss during treatment.[27,28] It is also significant that CRP/ALB ratio should be applied with a combination of the standard TNM staging system to better individualized treatment and surveillance of LSCC patients.

This study has several limitations. The retrospective nature of this study meant that many patients without their detailed medical records were excluded, which may lead to inevitable bias. Also, there may be other unknown factors that could influence serum CRP, ALB, and other biochemical factors. The area under the curve created by ROC curve was relatively low; a relatively small number of patients enrolled in this study may explain this. We also did not investigate the relationship between nutritional support therapy and CRP/ALB ratio in this study. A well-designed prospective study with a large cohort is required to solve these clinical as well as basic life science problems in order to provide a better answer to patients' prognosis in the future.

Conclusion

This is the first study showing that the CRP/ALB ratio is an independent prognostic factor for OS and DFS in patients with LSCC. As an easily accessible preoperative biomarker, its role in combination with the TNM staging system could be evaluated to predict a more accurate clinical outcome in LSCC patients in the future.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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