

The combination of preoperative serum C-reactive protein and carcinoembryonic antigen is a useful prognostic factor in patients with esophageal squamous cell carcinoma: a combined ROC analysis

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Background: The prognostic value of inflammatory index in esophageal cancer (EC) has not been established. In the present study, therefore, we initially evaluated a novel prognostic system, named the COCC (COmbination of C-reactive protein [CRP] and carcinoembryonic antigen [CEA]), for making a prognosis in patients with esophageal squamous cell carcinoma (ESCC).

Methods: A total of 327 patients with ESCC between January 2006 and December 2008 were included in this retrospective study. The COCC was calculated by combined CRP and CEA according to the logistic equation. The Kaplan–Meier method was used to calculate the cancer-specific survival (CSS), and the difference was assessed by the log-rank test. Cox regression analyses were performed to evaluate the prognostic factors.

Results: In our study, COCC was defined as $\text{CRP} + 0.71 \text{ CEA}$ according to the logistic equation. Receiver operating characteristic curves for CSS prediction were plotted to verify the optimum cutoff points for CRP, CEA, and COCC, which were 9.8 mg/L, 4.2 ng/mL, and 8.0, respectively. Patients with $\text{COCC} \leq 8.0$ had a significantly better CSS than patients with $\text{COCC} > 8.0$ (53.1% vs 15.3%, $P < 0.001$). Multivariate analysis revealed that COCC was an independent prognostic factor in patients with ESCC ($P = 0.006$). In addition, the area under the curve (AUC) was 0.722 for COCC, 0.645 for CRP, and 0.618 for CEA, indicating that COCC was superior to CRP or CEA for CSS prediction.

Conclusion: The COCC is an independent prognostic factor in patients with ESCC. We conclude that COCC was superior to CRP or CEA as a more precise prognostic factor in patients with ESCC.

Keywords: esophageal squamous cell carcinoma, C-reactive protein, carcinoembryonic antigen, cancer-specific survival, prognosis

Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, but the sixth leading cause of death due to cancer.¹ The most common histological types regarding EC are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).² In contrast to the predominance of EAC in the Western countries, ESCC accounts for more than 95% of ECs in People's Republic of China.^{2,3} Radical resection remains the treatment of choice; however, the prognosis is still poor in patients with EC.^{4,5} The histological types in ECs differ between People's Republic of China

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and Western countries, and therefore, a prognostic study that takes into account ESCC in People's Republic of China is more and more important.

In recent years, systemic inflammatory response (SIR) has been playing an important role in cancer.^{6,7} Serum C-reactive protein (CRP) is a sensitive indicator of SIR. Previous studies have shown that serum CRP was associated with prognosis in several cancers.⁸⁻¹⁰ Similar results were also found in ECs. This observation is in line with data from Nozoe et al,¹¹ Feng et al¹² and Ikeda et al.¹³ However, Zingg et al¹⁴ suggested that CRP is not an independent factor in EC patients who proceeded directly to surgery. Moreover, it was shown that trauma, renal and/or hepatic failure, and many inflammatory diseases may potentially affect the CRP.^{15,16} Therefore, CRP alone without other variables may not be associated with real prognosis. Thus, the prognostic value of serum CRP with other variables (such as tumor markers) may be a new research hotspot. Carcinoembryonic antigen (CEA) is the most widely used and readily available tumor marker for gastrointestinal cancer.^{17,18} In the present study, therefore, we initially evaluated a novel prognostic system, named the COCC (COmbination of CRP and CEA), for making a prognosis of patients with ESCC.

Patients and methods

A total of 327 consecutive patients with ESCC who underwent curative esophagectomy between January 2006 and December 2008 in Zhejiang Cancer Hospital (Hangzhou, People's Republic of China) were included in this retrospective study. All of the patients included in the analysis fit the criteria: 1) ESCC was confirmed by histopathology with curative esophagectomy; 2) patients without preoperative neoadjuvant therapy; 3) patients without previous anti-inflammatory medicines within 1 week; 4) patients without trauma, renal and/or hepatic failure, and other inflammatory diseases; and 5) preoperative serum CRP and CEA were obtained before esophagectomy within 1 week.

Serum CRP was determined by latex-enhanced homogeneous immunoassay. Serum CEA was detected by immunoradiometric assay. The cutoff values for CRP and CEA were 10 mg/L and 5 ng/mL, respectively. Based on our medical records, the following data were also collected for each patient: age, gender, tumor length and location, differentiation, T stage, and N stage. Ethical approval was obtained from the Ethical Committees of Zhejiang Cancer Hospital (Hangzhou, People's Republic of China). All of the patients included in the study were staged according to the

seventh edition of the American Joint Committee on Cancer (AJCC) Staging.¹⁹

Patients were followed up at our outpatient department every 3–6 months for the first 2 years, then annually. The last follow-up was on November 30, 2011. As this series described the prognosis of patients with ESCC, a cancer-specific survival (CSS) was ascertained in the current study. The CSS was defined as the time from surgery to cancer-related death.

Statistical analysis

Statistical evaluation was performed with SPSS 17.0 (Chicago, IL, USA). A logistic regression analysis was done to identify the CRP and CEA in the prognosis of ESCC and yield a logistic equation. The COCC was calculated by combined CRP and CEA according to the logistic equation. A receiver operating characteristic (ROC) curve for CSS prediction was plotted to verify the optimum cutoff point for CRP, CEA, and COCC. The area under the curve (AUC) was used as an estimation of diagnostic accuracy. Chi-squared test was used to determine the significance of differences for patients grouped by COCC. Pearson correlation analysis was performed to calculate the correlation among CRP, CEA, and COCC. The CSS was calculated by the Kaplan–Meier method, and the difference was assessed by the log-rank test. A univariate analysis was used to examine the prognostic predictors. Possible prognostic factors were considered in a multivariable analysis. A $P < 0.05$ was considered to be statistically significant.

Results

The baseline characteristics are shown in Table 1. Among the 327 patients, 41 (12.5%) were women and 286 (87.5%) were men. The mean age was 59.3 ± 7.8 years (ranges, 38–80 years). The mean CRP and CEA were 9.1 ± 14.9 mg/L and 3.5 ± 2.9 ng/mL, respectively. The positive rates for CRP and CEA were 27.8% (91/327) and 17.4% (57/327), respectively.

CRP and CEA were then extracted for logistic regression analysis to identify the positive prognosis. Subsequently, the logistic regression equation was as follows:

$$Y = 1.455 \text{ CRP} + 1.027 \text{ CEA} - 0.093.$$

Thus,

$$Y_{\text{COCC}} = \text{CRP} + 1.027/1.455 \text{ CEA} = \text{CRP} + 0.71 \text{ CEA}.$$

The histograms of CRP, CEA, and COCC are shown in Figure 1.

The ROC curves for survival prediction (CSS) were plotted to verify the optimum cutoff points for CRP, CEA,

Table 1 The baseline characteristics of patients in ESCC

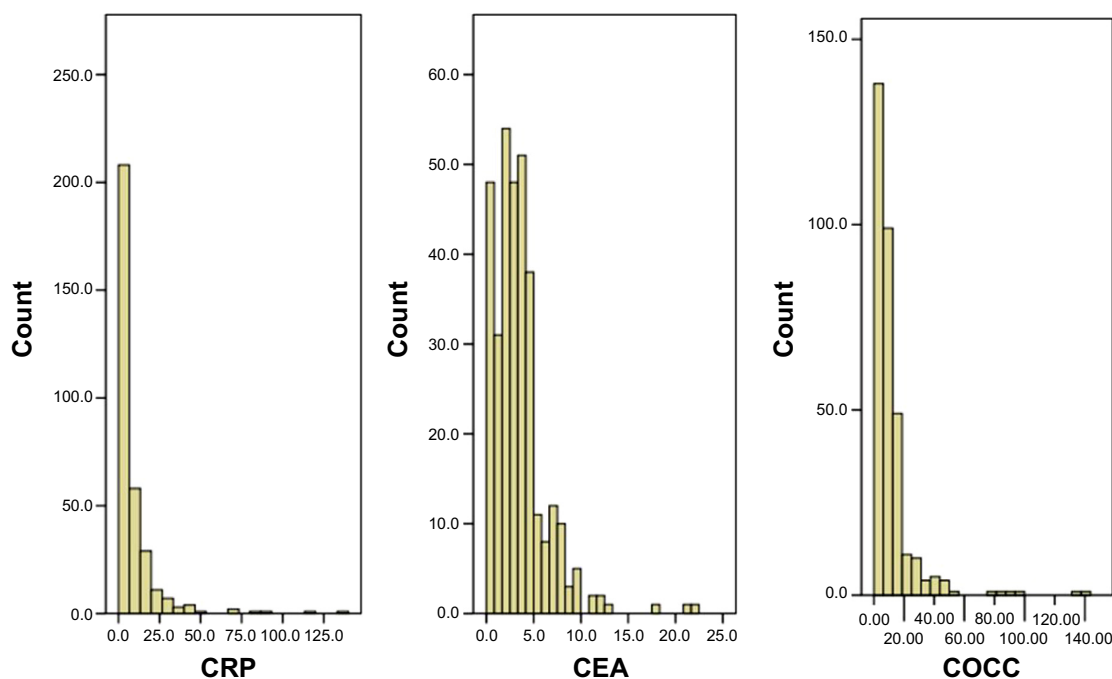
	Cases (n, %)
Age (mean \pm SD, years)	59.3 \pm 7.8
\leq 60	183 (56.0)
$>$ 60	144 (44.0)
Gender	
Female	41 (12.5)
Male	286 (87.5)
Tumor location	
Upper	16 (4.9)
Middle	159 (48.6)
Lower	152 (46.5)
Differentiation	
Well	48 (14.7)
Moderate	214 (65.4)
Poor	65 (19.9)
T stage	
T1	52 (15.9)
T2	55 (16.8)
T3	185 (56.6)
T4a	35 (10.7)
N stage	
N0	174 (53.2)
N1	88 (26.9)
N2	44 (13.5)
N3	21 (6.4)
CRP (mean \pm SD, mg/L)	9.1 \pm 14.9
CEA (mean \pm SD, ng/mL)	3.5 \pm 2.9

Abbreviations: ESCC, esophageal squamous cell carcinoma; SD, standard deviations; T, tumor; N, node; CRP, C-reactive protein; CEA, carcinoembryonic antigen.

and COCC, which were 9.8 mg/L, 4.2 ng/mL, and 8.0, respectively (Figure 2). The patients were then divided into two groups for further analysis (patients with COCC \leq 8.0 and patients with COCC $>$ 8.0). In our study, there were 196 (59.9%) patients with COCC \leq 8.0 and 131 (40.1%) patients with COCC $>$ 8.0. Our study demonstrated that COCC was associated with tumor length ($P=0.002$), differentiation ($P=0.035$), T stage ($P<0.001$), and N stage ($P=0.016$) (Table 2). In addition, our study showed that the values of COCC were higher in patients with high T stage and N stage (Figure 3).

Pearson correlation analysis was used to analyze the correlation of CRP, CEA, and COCC. Our results revealed that there were significant positive correlations between CRP and CEA ($r=0.386$, $P<0.001$, Figure 4A), CRP and COCC ($r=0.988$, $P<0.001$, Figure 4B), CEA and COCC ($r=0.492$, $P<0.001$, Figure 4C).

Patients with COCC \leq 8.0 had a significantly better CSS than patients with COCC $>$ 8.0 (53.1% vs 15.3%, $P<0.001$) (Figure 5A). There were also significant differences in CSS regarding CRP (46.6% vs 15.4%, $P<0.001$, Figure 5B) and CEA (45.1% vs 20.2%, $P=0.001$, Figure 5C). To assess the confounding effect of COCC on T stage and N stage, we further stratified patients into different groups corresponding to T stage (T1–T2 and T3–T4a) and N stage (N0 and N1–N3).

**Figure 1** The histograms of the CRP, CEA, and COCC.

Notes: The mean values for CRP, CEA, and COCC were 9.1 \pm 14.9 mg/L, 3.5 \pm 2.9 ng/mL, and 11.5 \pm 15.9, respectively.

Abbreviations: CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA.

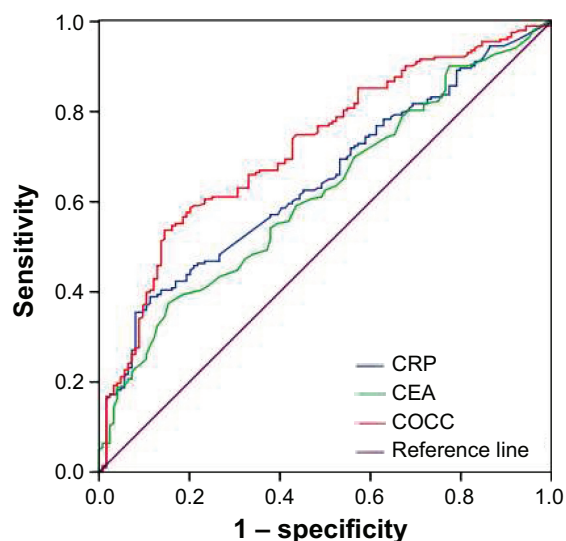


Figure 2 ROC curves for CSS prediction.

Notes: An ROC curve plots the sensitivity on the y-axis against one minus the specificity on the x-axis. A diagonal line at 45°, known as the line of chance, would result from a test that allocated subjects randomly. ROC curves for CSS were plotted to verify the optimum cutoff points for CRP, CEA, and COCC, which were 9.8 mg/L, 4.2 ng/mL, and 8.0, respectively. The AUC was 0.722 (95% CI: 0.666–0.778, $P < 0.001$) for COCC, 0.645 (95% CI: 0.586–0.705, $P < 0.001$) for CRP, and 0.618 (95% CI: 0.557–0.679, $P < 0.001$) for CEA.

Abbreviations: CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA; ROC, receiver operating characteristic; CSS, cancer-specific survival; AUC, area under the curve.

The predictive value of COCC was significant in patients with T1–T2 ($P = 0.010$), T3–T4a ($P < 0.001$), N0 ($P < 0.001$), and N1–N3 ($P < 0.001$) (Figure 6).

In univariate analysis, we found that tumor length ($P < 0.001$), vessel invasion ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), CRP ($P < 0.001$), CEA ($P = 0.001$), and COCC ($P < 0.001$) had significant associations with CSS (Table 3). The multivariate Cox proportional hazards model demonstrated that COCC was an independent prognostic factor in patients with ESCC (Table 3). COCC > 8.0 had a hazard ratio (HR) of 1.809 [95% confidence interval (CI): 1.190–2.751, $P = 0.006$] for CSS (Table 4).

The AUC was 0.722 (95% CI: 0.666–0.778, $P < 0.001$) for COCC, 0.645 (95% CI: 0.586–0.705, $P < 0.001$) for CRP, and 0.618 (95% CI: 0.557–0.679, $P < 0.001$) for CEA, indicating that COCC was superior to CRP or CEA and could be used as a more precise prognostic model for ESCC patients (Figure 2).

Discussion

In the present study, we initially evaluated the novel prognostic model (COCC) in patients with ESCC. Our study

Table 2 Comparison of baseline clinical characteristics based on COCC

	COCC ≤ 8.0 (n, %)	COCC > 8.0 (n, %)	P-value
Age (years)			
≤ 60	113 (57.7)	70 (53.4)	0.452
> 60	83 (42.3)	61 (46.6)	
Gender			
Female	25 (12.8)	16 (12.2)	0.885
Male	171 (87.2)	115 (87.8)	
Tumor length (cm)			
≤ 3	65 (33.2)	23 (17.6)	0.002
> 3	131 (66.8)	108 (82.4)	
Tumor location			
Upper	10 (5.1)	6 (4.6)	0.064
Middle	85 (43.4)	74 (56.5)	
Lower	101 (51.5)	51 (38.9)	
Vessel invasion			
Negative	168 (85.7)	108 (82.4)	0.424
Positive	28 (14.3)	23 (17.6)	
Differentiation			
Well	32 (16.3)	16 (12.2)	0.035
Moderate	134 (68.4)	80 (61.1)	
Poor	30 (15.3)	35 (26.7)	
T stage			
T1	41 (20.9)	11 (8.4)	0.001
T2	38 (19.4)	17 (13.0)	
T3	103 (52.6)	82 (62.6)	
T4a	14 (7.1)	21 (16.0)	
N stage			
N0	116 (59.2)	58 (44.3)	0.016
N1	50 (25.5)	38 (29.0)	
N2	18 (9.2)	26 (19.8)	
N3	12 (6.1)	9 (6.9)	

Note: The bold values indicate < 0.05 .

Abbreviations: COCC, COmbination of CRP and CEA; T, tumor; N, node.

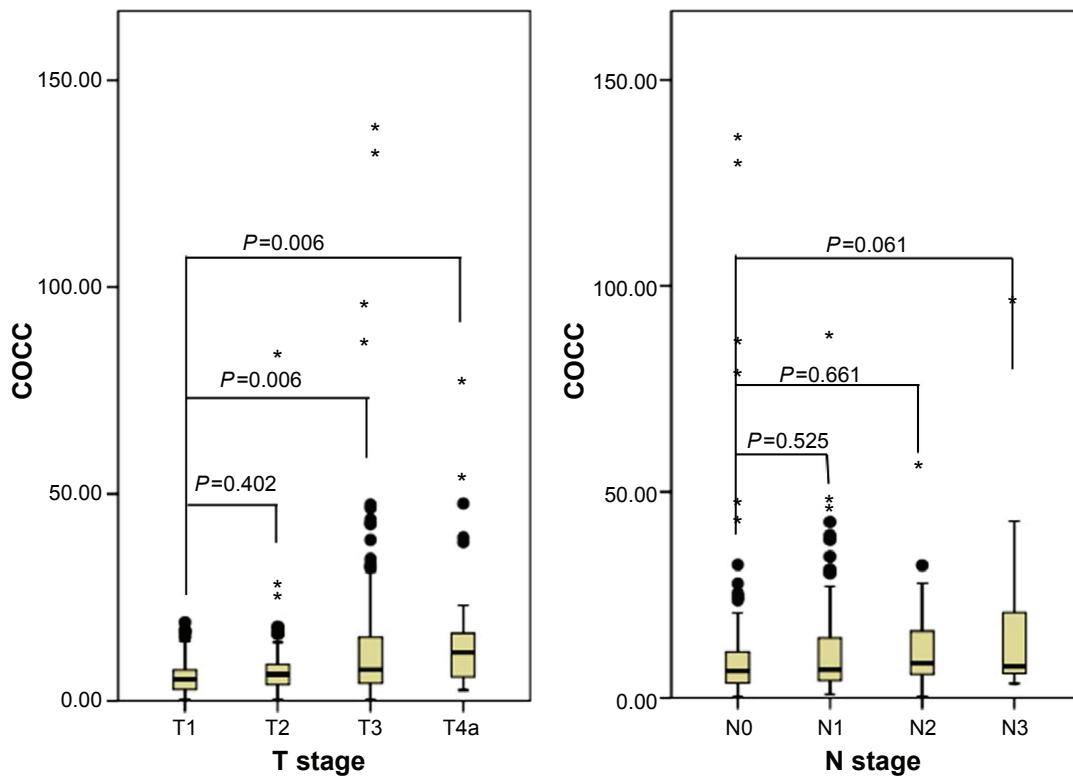


Figure 3 The values of COCC in patients with different T stages and N stages.
Notes: The mean values of COCC for T1, T2, T3, and T4a were 6.23 ± 4.71 , 8.78 ± 11.99 , 13.05 ± 18.26 , and 15.71 ± 16.46 , respectively. The mean values of COCC for N0, N1, N2, and N3 were 10.58 ± 17.35 , 11.89 ± 13.57 , 11.75 ± 9.61 , and 17.46 ± 21.62 , respectively.
Abbreviations: COCC, COmbination of CRP and CEA; T, tumor; N, node.

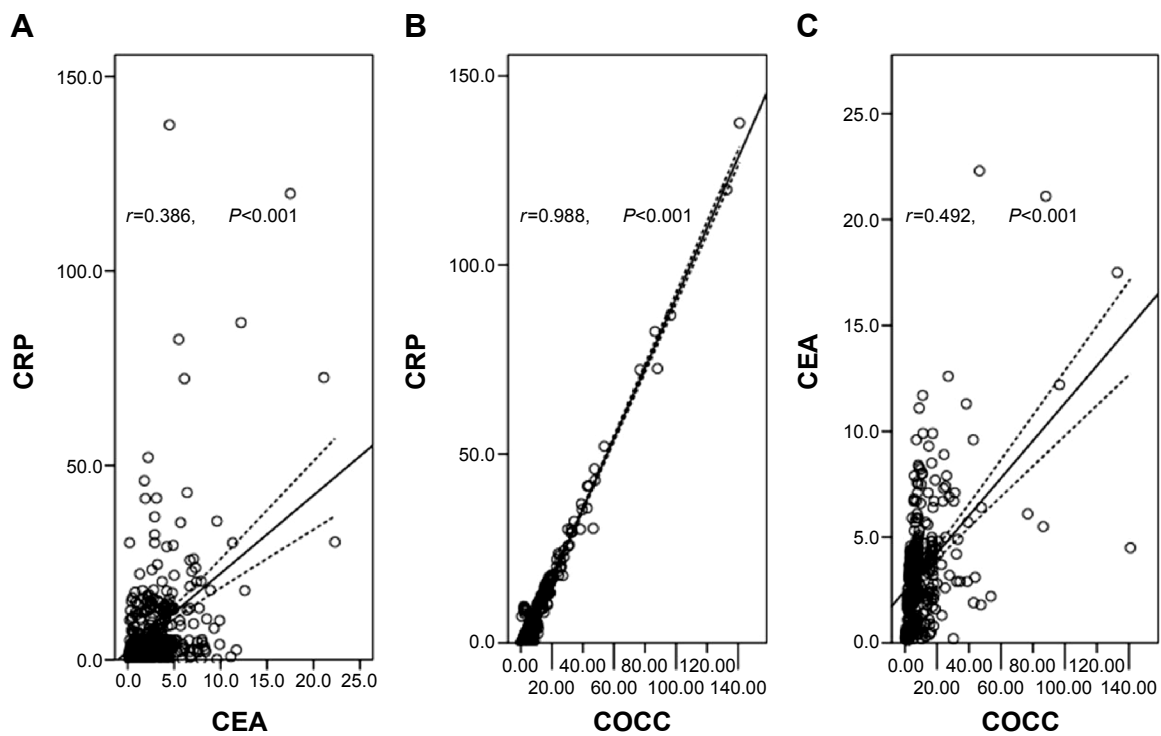


Figure 4 Pearson correlation analysis.
Notes: There were significant positive correlations between CRP and CEA ($r=0.386$, $P<0.001$; **A**), CRP and COCC ($r=0.988$, $P<0.001$; **B**), CEA and COCC ($r=0.492$, $P<0.001$; **C**).
Abbreviations: CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA.

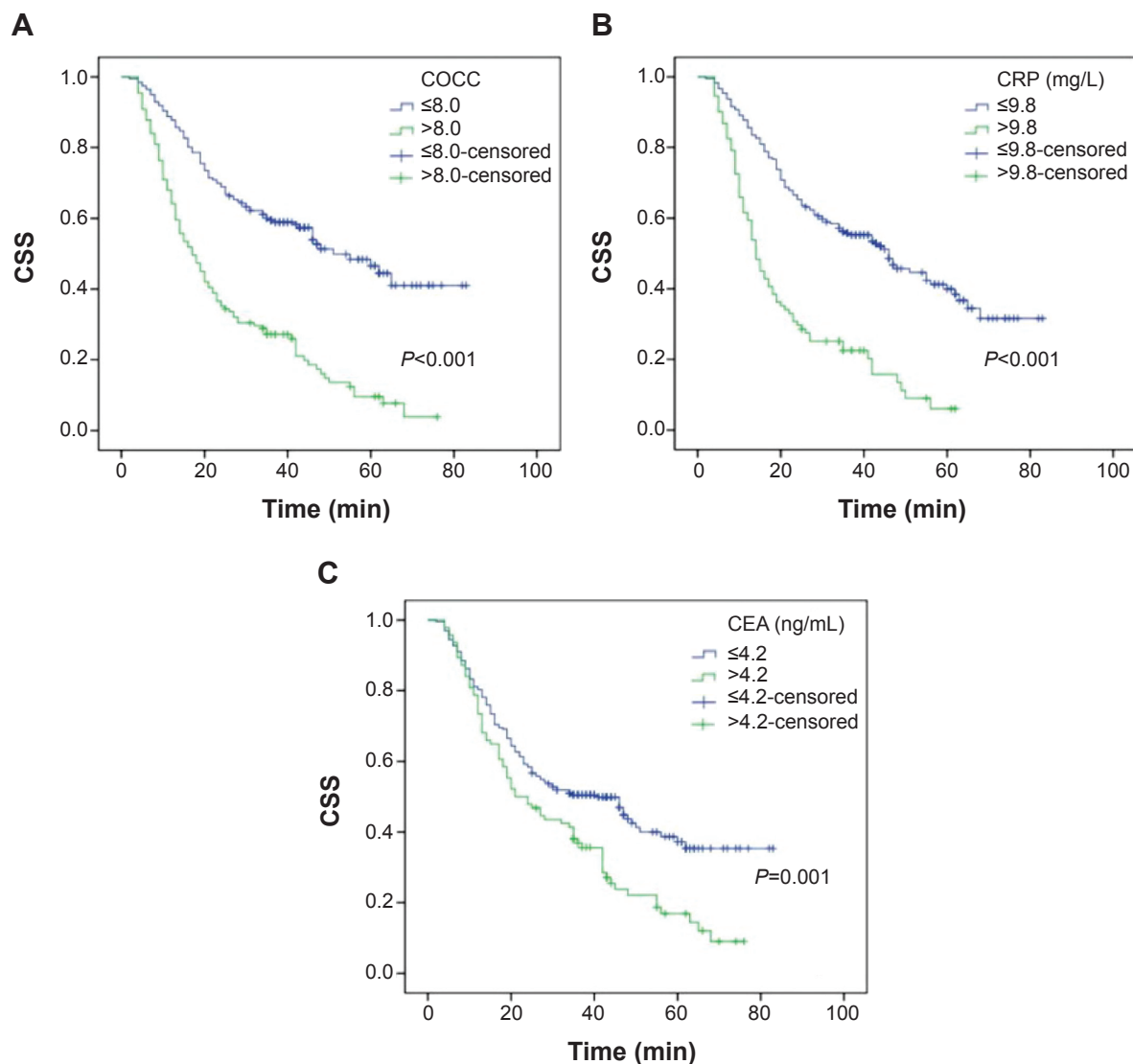


Figure 5 Kaplan–Meier CSS curves stratified by CRP, CEA, and COCC.

Notes: Patients with COCC ≤ 8.0 had a significantly better CSS than patients with COCC > 8.0 (53.1% vs 15.3%, $P < 0.001$; **A**). There were also significant differences in CSS regarding CRP (46.6% vs 15.4%, $P < 0.001$; **B**) and CEA (45.1% vs 20.2%, $P = 0.001$; **C**).

Abbreviations: CSS, cancer-specific survival; CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA.

demonstrated that COCC is associated with cancer prognosis and can be considered as an independent prognostic marker in patients with ESCC. We used an ROC curve for CSS prediction to verify the optimal cutoff point. In our study, we concluded that the value of 8.0 may be the optimum cutoff point for COCC in predicting CSS in patients with ESCC. We conclude COCC was superior to CRP or CEA as a more precise prognostic factor in patients with ESCC.

Serum tumor marker plays an important role in cancer diagnosis and prognosis. CEA is the most widely used and readily available tumor marker for gastrointestinal cancer.^{17,18} To date, there have been few studies regarding CEA in patients with EC mainly because of its low sensitivity and

specificity. In our study, the positive rate for CEA in patients with ESCC was 17.4%. Thus, we used an ROC curve for CSS prediction to verify the optimal cutoff point for CEA, which was 4.2 ng/mL. Previous studies have demonstrated the efficacy of CEA as a diagnostic and prognostic marker in patients with EC.^{20,21} In our study, there were significant differences in CSS regarding CEA (45.1% vs 20.2%, $P = 0.001$). However, CEA was not an independent prognostic factor in patients with ESCC ($P = 0.818$).

There is a strong linkage between inflammation and cancer. In the current study, we analyzed the prognostic value of COCC in patients with ESCC without preoperative neoadjuvant therapy mainly because chemotherapy and/or

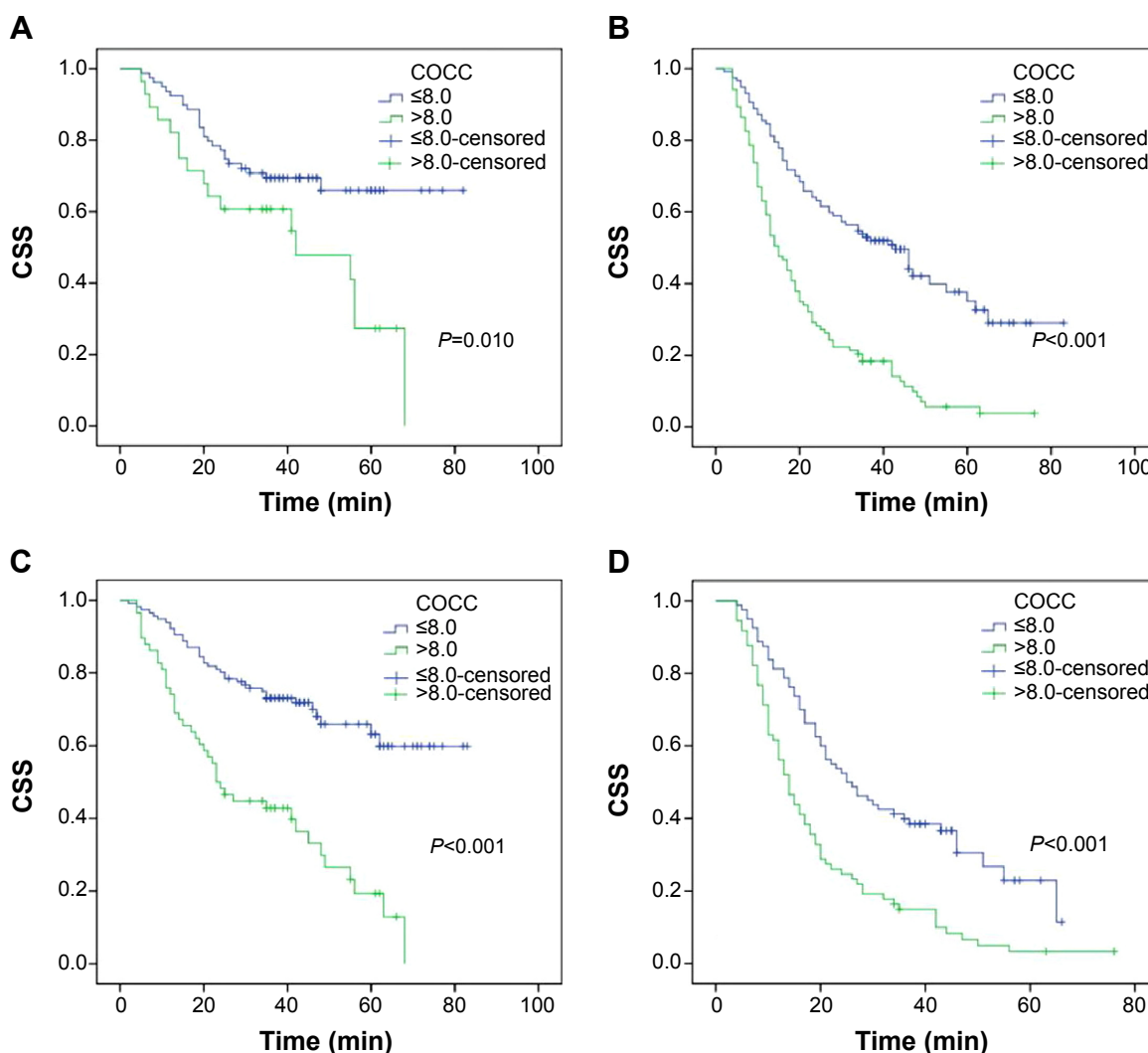


Figure 6 Kaplan-Meier CSS curves stratified by COCC in patients with T stage and N stage.

Notes: The predictive value of COCC was significant in patients with T1–T2 ($P=0.010$, **A**), T3–T4a ($P<0.001$, **B**), N0 ($P<0.001$, **C**), and N1–N3 ($P<0.001$, **D**).

Abbreviations: CSS, cancer-specific survival; COCC, COmbination of CRP and CEA; T, tumor; N, node.

radiation will have an important impact on the SIR. CRP is a very sensitive indicator of SIR. Previous published studies have shown that serum CRP is a significant prognostic indicator in several cancers.^{8–10} However, its role in EC is still controversial.^{11–14} In addition, several studies have demonstrated that trauma, renal and/or hepatic failure, and many inflammatory diseases may potentially affect the CRP.^{15,16} Therefore, the CRP may be considered insufficient for prognostication.

In the current study, therefore, we initially conducted a study to determine whether the novel prognostic model (COCC) is useful for predicting CSS in patients with ESCC. Thus, we used an ROC curve for CSS prediction to verify the optimal cutoff point for COCC, which was 8.0. In our study, Kaplan-Meier analysis showed that COCC was able to

divide such patients into two independent groups ($P<0.001$). Then multivariate analysis demonstrated that COCC was an independent prognostic factor in patients with ESCC ($P=0.006$). In addition, our study showed a better discrimination for COCC in terms of HR than CRP and CEA. The AUC of the COCC was the largest (Figure 2), indicating that COCC was superior to CRP or CEA as a predictive factor in patients with ESCC. In the further investigation, subgroup analysis was also performed. In our study, the predictive value of COCC was also significant in patients with T1–T2 ($P=0.010$), T3–T4a ($P<0.001$), N0 ($P<0.001$), and N1–N3 ($P<0.001$) (Figure 5).

Several limitations should be acknowledged in the current study. First, the current study was a retrospective study with a small sample and short duration of the mean follow-up.

Table 3 Univariate analyses of CSS in ESCC patients

	CSS (%)	P-value	HR (95% CI)	P-value
Age (years)				
≤60	38.8	0.543	1.000	0.547
>60	36.8		1.089 (0.825–1.436)	
Gender				
Female	43.9	0.425	1.000	0.431
Male	37.1		1.191 (0.771–1.838)	
Tumor length (cm)				
≤3	54.5	<0.001	1.000	<0.001
>3	31.8		2.048 (1.446–2.902)	
Tumor location				
Upper/middle	41.7	0.264	1.000	0.270
Lower	33.6		1.167 (0.833–1.394)	
Vessel invasion				
Negative	41.7	<0.001	1.000	<0.001
Positive	17.6		1.971 (1.400–2.774)	
Differentiation				
Well/moderate	39.1	0.119	1.000	0.124
Poor	33.3		1.300 (0.930–1.816)	
T stage				
T1–T2	60.7	<0.001	1.000	<0.001
T3–T4	26.8		2.523 (1.795–3.546)	
N stage				
N0	54.6	<0.001	1.000	<0.001
N1–N3	19.0		2.717 (2.040–3.618)	
Adjuvant therapy				
No	39.4	0.236	1.000	0.242
Yes	34.7		1.192 (0.888–1.600)	
CRP (mg/L)				
≤9.8	46.6	<0.001	1.000	<0.001
>9.8	15.4		2.821 (2.111–3.770)	
CEA (ng/mL)				
≤4.2	45.1	0.001	1.000	0.001
>4.2	20.2		1.616 (1.215–2.150)	
COCC				
≤8.0	53.1	<0.001	1.000	<0.001
>8.0	15.3		2.804 (2.121–3.707)	

Note: The bold values indicate <0.05.

Abbreviations: CSS, cancer-specific survival; ESCC, esophageal squamous cell carcinoma; T, tumor; N, node; CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA; HR, hazard ratio; CI, confidence interval.

Table 4 Multivariate analyses of CSS in ESCC patients

	HR (95% CI)	P-value
Tumor length (>3 vs ≤3 cm)	1.240 (0.838–1.834)	0.282
Vessel invasion (positive vs negative)	1.341 (0.936–1.921)	0.109
T stage (T3–T4a vs T1–T2)	1.546 (1.047–2.282)	0.028
N stage (N1–N3 vs N0)	1.999 (1.454–2.747)	<0.001
CRP (>9.8 vs ≤9.8 mg/L)	1.627 (1.072–2.471)	0.022
CEA (>4.2 vs ≤4.2 ng/mL)	1.037 (0.762–1.411)	0.818
COCC (>8.0 vs ≤8.0)	1.809 (1.190–2.751)	0.006

Note: The bold values indicate <0.05.

Abbreviations: CSS, cancer-specific survival; ESCC, esophageal squamous cell carcinoma; T, tumor; N, node; CRP, C-reactive protein; CEA, carcinoembryonic antigen; COCC, COmbination of CRP and CEA; HR, hazard ratio; CI, confidence interval.

Second, the current study used data from a single institution, but without a control group, there may have been a lack of uniformity. Third, patients who had neoadjuvant chemotherapy and/or radiotherapy were excluded from the current study, which may have influenced our analysis. Therefore, further studies are needed to illuminate the relationship between COCC and prognosis in patients with ESCC.

Conclusion

In summary, our study showed that COCC is associated with prognosis and can be considered as an independent prognostic

marker in patients who underwent esophagectomy for ESCC. We conclude that COCC was superior to CRP or CEA as a more precise prognostic factor in patients with ESCC.

Disclosure

The authors report no conflicts of interest in this work.

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