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The Combination of Platelet Count and Neutrophil Lymphocyte Ratio Is a Predictive Factor in Patients with Esophageal Squamous Cell Carcinoma

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Abstract

OBJECTIVE: The prognostic value of inflammation indexes in esophageal cancer was not established. In this study, therefore, both prognostic values of Glasgow prognostic score (GPS) and combination of platelet count and neutrophil lymphocyte ratio (COP-NLR) in patients with esophageal squamous cell carcinoma (ESCC) were investigated and compared. *METHODS:* This retrospective study included 375 patients who underwent esophagectomy for ESCC. The cancer-specific survival (CSS) was calculated by the Kaplan-Meier method, and the difference was assessed by the log-rank test. The GPS was calculated as follows: patients with elevated C-reactive protein (>10 mg/l) and hypoalbuminemia (<35 g/l) were assigned to GPS2. Patients with one or no abnormal value were assigned to GPS1 or GPS0, respectively. The COP-NLR was calculated as follows: patients with elevated platelet count (>300 × 10^9/l) and neutrophil lymphocyte ratio (>3) were assigned to COP-NLR2. Patients with one or no abnormal value were assigned to COP-NLR1 or COP-NLR0, respectively. *RESULTS:* The 5-year CSS in patients with GPS0, 1, and 2 was 50.0%, 27.0%, and 12.5%, respectively ($P < .001$). The 5-year CSS in patients with COP-NLR0, 1, and 2 was 51.8%, 27.0%, and 11.6%, respectively ($P < .001$). Multivariate analysis showed that both GPS ($P = .003$) and COP-NLR ($P = .003$) were significant predictors in such patients. In addition, our study demonstrated a similar hazard ratio (HR) between COP-NLR and GPS (HR = 1.394 *vs* HR = 1.367). *CONCLUSIONS:* COP-NLR is an independent predictive factor in patients with ESCC. We conclude that COP-NLR predicts survival in ESCC similar to GPS.

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of death from cancer [1]. Squamous cell carcinoma (SCC) comprises about 80% of all ECs worldwide [2]. In China, SCC is the most common pathologic type of ECs, in contrast to the predominance of adenocarcinoma in the Western countries [3,4]. There are important biologic differences between China and Western countries regarding ECs; therefore, a prognostic study that takes into account SCC in China is necessary.

Recently, systemic inflammatory response plays an important role in the progression of cancer [5,6]. Previous studies have shown that serum C-reactive protein (CRP) influenced the prognosis in patients with gastrointestinal cancers [7]. Moreover, the Glasgow prognostic score (GPS) combines serum CRP and hypoalbuminemia and has been demonstrated to be a predictive factor in various cancers, including ECs [8–10]. In addition, there is an increasing evidence

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that platelet count and neutrophil lymphocyte ratio (NLR) can be used for prognostication in several cancers [11,12]. Recently, Ishizuka et al. [13] evaluated a novel inflammation-based prognostic system, termed as the combination of platelet count and NLR (COP-NLR). They demonstrated that COP-NLR is a useful predictor of postoperative survival in patients with colorectal cancer [13]. However, to the best of our knowledge, no studies regarding COP-NLR in patients with EC are available. Therefore, the aim of this study was to investigate and compare the prognostic values of COP-NLR and GPS in patients with esophageal squamous cell carcinoma (ESCC).

Methods

Patients

From January 2006 to December 2008, a retrospective analysis was conducted in 375 patients with ESCC who underwent curative esophagectomy at Zhejiang Cancer Hospital. All of the patients included in the analysis fit the following criteria: 1) ESCC confirmed by histopathology, 2) surgery with curative esophagectomy, 3) at least six lymph nodes were examined for pathologic diagnosis, and 4) surgery was neither preceded nor followed by adjuvant chemotherapy and/or radiotherapy.

On the basis of the medical records, the following data were collected for each patient: age, gender, laboratory examination, differentiation, tumor length and location, depth of invasion, nodal metastasis, and other miscellaneous characteristics. Ethical approval was obtained from the Ethical Committees of Zhejiang Cancer Hospital. All of the patients included in the study were staged according to the seventh edition of the American Joint Committee on Cancer Cancer Staging Manual [14].

In our institute, patients were followed up in the outpatient department. X-ray or computed tomography of the chest was performed during the follow-up. As this study described the prognosis of patients with ESCC, therefore, a cancer-specific survival (CSS) analysis would be more appropriate. Therefore, the CSS was ascertained in this study. The last follow-up time was November 2011.

GPS and COP-NLR Evaluation

Routine laboratory measurements including the serum levels of CRP, albumin, and blood cell counts were extracted in a retrospective fashion from the medical records. GPS was calculated as follows: patients with elevated CRP (>10 mg/l) and hypoalbuminemia (<35 g/l) were assigned to GPS2. Patients with one or no abnormal value were assigned to GPS1 or GPS0, respectively [8]. COP-NLR was calculated as follows: patients with elevated platelet count level ($>300 \times 10^9$/l) and NLR (>3) were assigned to COP-NLR2. Patients with one or no abnormal value were assigned to COP-NLR1 or COP-NLR0, respectively [13].

Statistical Analysis

Statistical evaluation was conducted with SPSS 17.0 (Chicago, IL). The Pearson Chi-squared test was used to determine the significance of differences. Correlation analysis was performed by Pearson and Spearman correlation analyses. 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 association between various prognostic predictors and CSS. Possible prognostic factors associated with CSS on univariate analysis were considered in a multivariable Cox proportional hazards regression analysis with the enter method. Moreover, the Akaike information criterion (AIC) and Bayesian information criteria (BIC) were used to identify the statistical model [15,16]. AIC was defined as AIC = −2log(maximum likelihood) + 2 × (the number of parameters in the model). BIC was defined as BIC = −2log(maximum likelihood) + (the number of parameters in the model) × log(sample size). A smaller AIC or BIC value indicates a more desirable model for predicting the outcome. A P value less than .05 was considered to be statistically significant.

Results

Patient Characteristics

Among the 375 patients with ESCC, 49 (13.1%) were women and 326 (86.9%) were men. The mean age was 59.1 ± 7.8 years, with an age range from 36 to 80 years. All of the clinicopathologic characteristics were comparable between patients grouped by GPS and COP-NLR, as shown in Tables 1 and 2. There were significant differences between the GPS and COP-NLR groups in tumor length ($P<.001$), depth of invasion ($P<.001$), and nodal metastasis ($P<.001$). In addition, an elevated COP-NLR was also associated with higher differentiation ($P=.006$).

Cancer-Specific Survival

The 5-year CSS was 38.1% in our study. The 5-year CSS in patients with GPS0, 1, and 2 was 50.0%, 27.0%, and 12.5%, respectively (GPS0 *vs* GPS1, $P<.001$; GPS1 *vs* GPS2, $P=.035$; Figure 1). The 5-year CSS in patients with COP-NLR0, 1, and 2 was 51.8%, 27.0%, and 11.6%, respectively (COP-NLR0 *vs* COP-NLR1, $P<.001$; COP-NLR1 *vs* COP-NLR2, $P=.005$; Figure 2).

Prognostic Factors

By univariate analysis, we found that seven clinicopathologic variables had significant associations with CSS (Table 3). Then, all of

Table 1. The Characteristics of the 375 SCCE Patients Grouped by GPS

	GPS0 (*n*)	GPS1 (*n*)	GPS2 (*n*)	*P* Value
Age (years)				.697
≤60	125	63	26	
>60	87	52	22	
Gender				.245
Female	32	14	3	
Male	180	101	45	
Tumor length (cm)				<.001
≤3	71	25	3	
>3	141	90	45	
Tumor location				.193
Upper	9	7	4	
Middle	93	61	26	
Lower	110	47	18	
Vessel involvement				.101
Negative	183	90	37	
Positive	29	25	11	
Perineural invasion				.226
Negative	177	92	35	
Positive	35	23	13	
Differentiation				.273
Well	32	13	7	
Moderate	144	75	27	
Poor	36	27	14	
Depth of invasion				<.001
T1	49	13	1	
T2	41	17	4	
T3	108	67	35	
T4	14	18	8	
Nodal metastasis				<.001
Negative	128	56	15	
Positive	84	59	33	

Table 2. The Characteristics of the 375 SCCE Patients Grouped by COP-NLR

	COP-NLR0 (*n*)	COP-NLR1 (*n*)	COP-NLR2 (*n*)	*P* Value
Age (years)				.576
≤60	107	83	24	
>60	88	54	19	
Gender				.287
Female	30	13	6	
Male	165	124	37	
Tumor length (cm)				<.001
≤3	74	21	4	
>3	121	116	39	
Tumor location				.785
Upper	10	9	1	
Middle	92	68	20	
Lower	93	60	22	
Vessel involvement				.688
Negative	164	112	34	
Positive	31	25	9	
Perineural invasion				.531
Negative	161	107	36	
Positive	34	30	7	
Differentiation				.006
Well	23	24	5	
Moderate	142	82	22	
Poor	30	31	16	
Depth of invasion				<.001
T1	48	12	3	
T2	38	19	5	
T3	96	86	28	
T4	13	20	7	
Nodal metastasis				<.001
Negative	119	68	12	
Positive	76	69	31	

the seven significant variables above were included in a multivariate Cox proportional hazards model. In that model, we demonstrated that both the GPS (P = .003) and the COP-NLR (P = .003) were significant independent predictors of CSS (Table 4). In addition, our study showed a similar hazard ratio (HR) between COP-NLR and GPS (HR = 1.394 *vs* HR = 1.367).

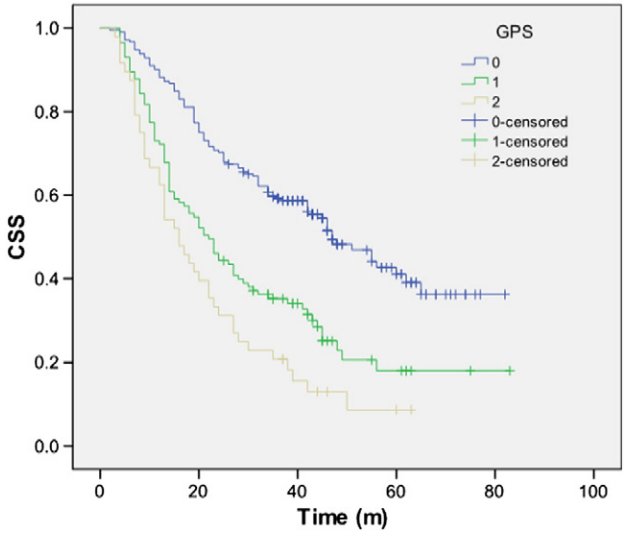

Figure 1. The 5-year CSS in patients with GPS0, 1, and 2 was 50.0%, 27.0%, and 12.5%, respectively (GPS0 *vs* GPS1, P < .001; GPS1 *vs* GPS2, P = .035).

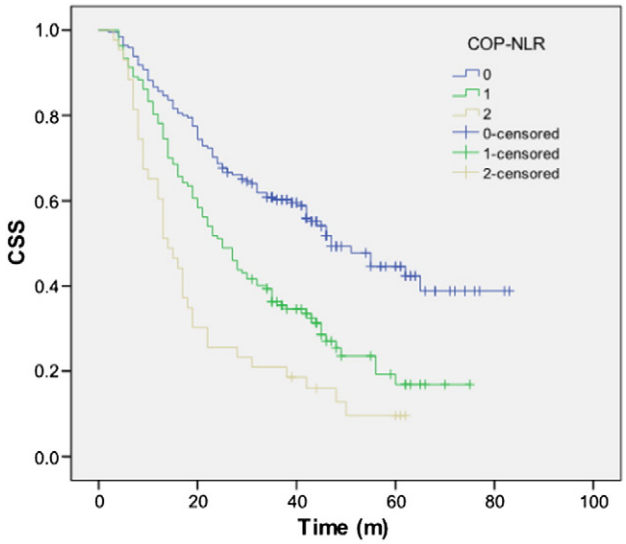

Figure 2. The 5-year CSS in patients with COP-NLR0, 1, and 2 was 51.8%, 27.0%, and 11.6%, respectively (COP-NLR0 *vs* COP-NLR1, P < .001; COP-NLR1 *vs* COP-NLR2, P = .005).

Correlation Analysis

There were significant positive correlations between COP-NLR and GPS (r = 0.494, P < .001). Our results showed significant negative correlations between CRP and albumin (r = −0.300, P < .001;

Table 3. Univariate Analyses in Patients with ESCC

	5-Year CSS (%)	Chi-Square	*P* Value	HR (95% CI)	*P* Value
Age (years)		0.074	.785		.787
≤60	38.3			1.000	
>60	37.9			1.036 (0.799-1.344)	
Gender		0.761	.383		.389
Female	44.9			1.000	
Male	37.1			1.193 (0.799-1.782)	
Tumor length (cm)		16.001	<.001		<.001
≤3	53.5			1.000	
>3	32.6			1.903 (1.376-2.632)	
Tumor location		0.327	.568		.572
Upper/middle	40.0			1.000	
Lower	36.0			1.077 (0.833-1.394)	
Vessel involvement		11.874	.001		.001
Negative	41.6			1.000	
Positive	21.5			1.709 (1.251-2.334)	
Perineural invasion		6.453	.011		.013
Negative	41.4			1.000	
Positive	25.4			1.479 (1.088-2.011)	
Differentiation		3.777	.052		.055
Well/moderate	39.2			1.000	
Poor	32.9			1.355 (0.993-1.850)	
Depth of invasion		27.016	<.001		<.001
T1-2	58.2			1.000	
T3-4	28.5			2.216 (1.623-3.024)	
Nodal metastasis		60.200	<.001		<.001
Negative	54.8			1.000	
Positive	19.3			2.735 (2.094-3.573)	
GPS		51.088	<.001		<.001
0	50.0			1.000	
1	27.0			2.075 (1.556-2.768)	
2	12.5			3.107 (2.166-4.456)	
COP-NLR		46.603	<.001		<.001
0	51.8			1.000	
1	27.0			1.909 (1.439-2.532)	
2	11.6			3.261 (2.230-4.767)	

Table 4. Multivariate Analyses in Patients with ESCC

	HR (95% CI)	*P* Value
Tumor length (>3 cm *vs* ≤3 cm)	1.033 (0.716-1.490)	.862
Vessel involvement (positive *vs* negative)	1.035 (0.742-1.442)	.841
Perineural invasion (positive *vs* negative)	1.128 (0.821-1.550)	.458
Depth of invasion (T3-4a *vs* T1-2)	1.459 (1.018-2.091)	.040
Nodal metastasis (positive *vs* negative)	2.109 (1.567-2.837)	<.001
GPS (1-2 *vs* 0)	1.367 (1.114-1.677)	.003
COP-NLR (1-2 *vs* 0)	1.394 (1.120-1.735)	.003

Figure 3*A*), NLR and albumin ($r = -0.148$, $P = .004$; Figure 3*E*), and platelet count and albumin ($r = -0.210$, $P < .001$; Figure 3*F*). There were significant positive correlations between CRP and NLR ($r = 0.157$, $P = .002$; Figure 3*B*) and CRP and platelet count ($r = 0.138$, $P = .007$; Figure 3*C*). However, there were no correlation between NLR and platelet count ($r = 0.079$, $P = .125$; Figure 3*D*).

AIC and BIC Analyses

AIC and BIC values were calculated by using logistic regression according to the survival status of patients when the follow-up was over. The AIC and BIC values were similar between COP-NLR and

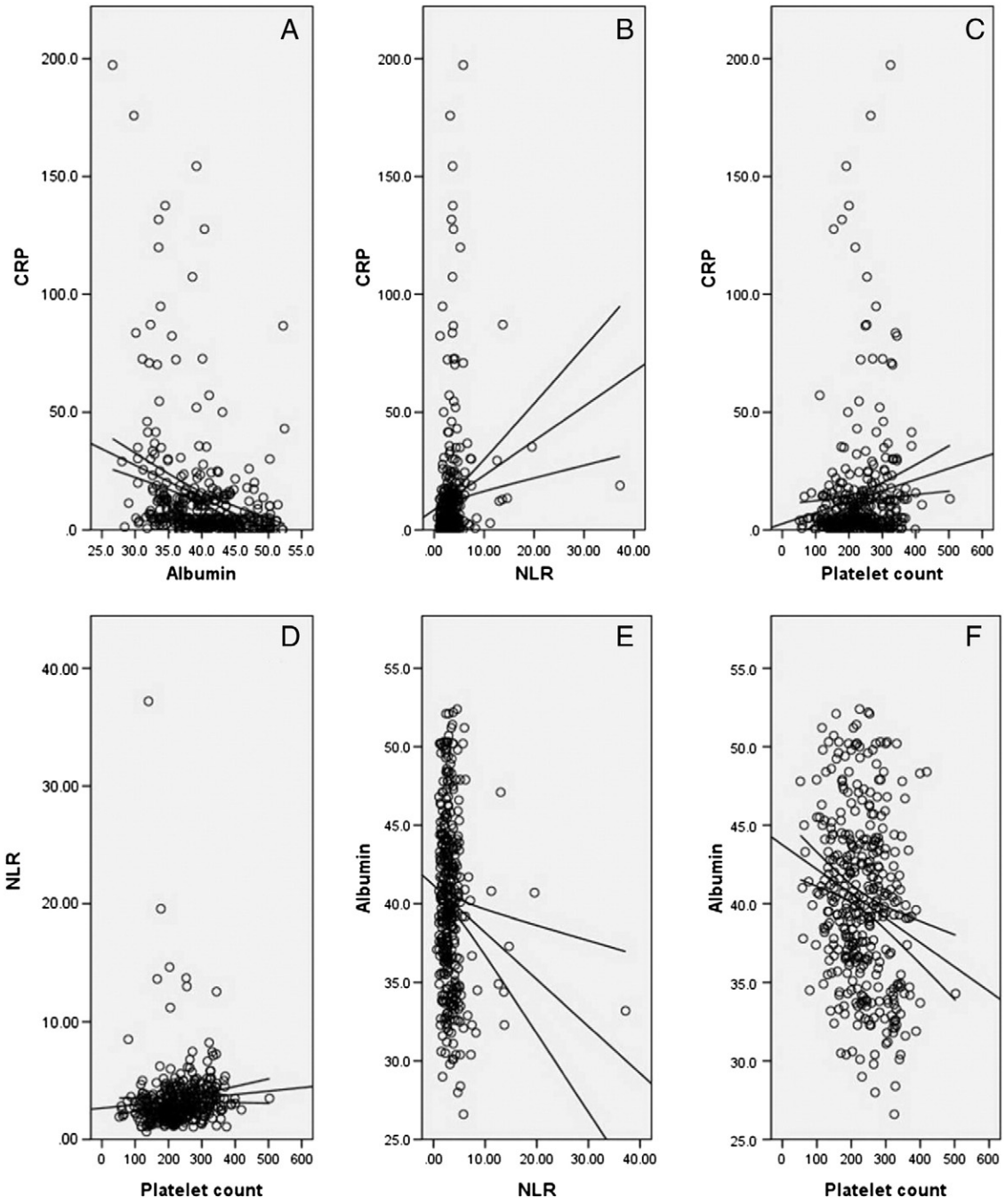

Figure 3. Negative correlations between CRP and albumin (A), NLR and albumin (E), and platelet count and albumin (F). Positive correlations between CRP and NLR (B) and CRP and platelet count (C). No correlation between NLR and platelet count (D).

Table 5. AIC and BIC Analyses in Patients with ESCC

	AIC	BIC	−2Log(Maximum Likelihood)
GPS	472.120	487.808	464.120
COP-NLR	468.824	484.532	460.824

GPS, indicating that COP-NLR predicts survival in ESCC similar to GPS (Table 5).

Discussion

There is strong linkage between inflammation and cancer [5,6]. In our study, we analyze the potential prognostic values of COP-NLR and GPS in ESCC patients without adjuvant chemoradiotherapy mainly because chemotherapy or radiation will have an important impact on the systemic inflammation. To the best of our knowledge, this is the first study to show COP-NLR as an independent prognostic factor in patients with ESCC. Our study showed that both GPS ($P = .003$) and COP-NLR ($P = .003$) were significantly associated with CSS in multivariate analysis. We conclude that COP-NLR is an independent predictive factor in patients with ESCC, and it predicts survival similar to GPS.

There are now a number of well-established systemic inflammation-based prognostic indexes for patients with EC. In particular, the GPS has been well validated. Several previous studies have shown that GPS is associated with survival in various cancers, including ECs [8–10]. Our study showed that GPS was associated with tumor size, depth of invasion, and nodal metastasis. This observation is in line with data from Vashist et al. [8] but is contrary to the result of Kobayashi et al. [9], who suggested that GPS has no significant correlation with the above clinicopathologic factors. Moreover, our study demonstrated that COP-NLR is an independent predictive factor in patients with ESCC, and the result was consistent with previous studies [8,9]. However, some of the previous reports using the GPS had several problems [17–19]. Therefore, the GPS may be considered insufficient for prognostication.

There is an increasing evidence that platelet count and NLR can be used for prognostication in patients with several types of cancer [11,12]. Recently, Ishizuka et al. [13] showed that COP-NLR is considered to be a useful predictor of postoperative survival in patients with colorectal cancer. They showed that COP-NLR is easy to measure routinely because of its low cost and convenience [13]. Therefore, we conducted a study to determine whether COP-NLR is useful for predicting long-term survival in patients with ESCC. In our study, we demonstrated that COP-NLR ($P = .003$) was significantly associated with CSS. Moreover, our study showed a similar HR between COP-NLR and GPS. In addition, the AIC and BIC values were similar between COP-NLR and GPS, indicating that COP-NLR predicts survival in ESCC similar to GPS.

The potential limitations of the present study include the use of a retrospective analysis and the short duration of the mean follow-up duration. In addition, we excluded patients who had adjuvant chemotherapy and/or radiotherapy, which may have influenced our analysis. Furthermore, AIC and BIC values were not correct if follow-up differed between patients, and the results of the study should therefore be regarded with caution. Thus, larger prospective studies will need to be performed to confirm these preliminary results.

Conclusion

In summary, our study showed that both GPS and COP-NLR are associated with tumor progression and can be considered as independent markers in patients with ESCC. We conclude that COP-NLR predicts survival in ESCC similar to GPS. However, larger prospective studies will need to be performed to confirm these preliminary results.

Competing Interests

The authors declare that they have no competing interests.

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