Original Article

Platelet-to-lymphocyte ratio is an independent prognosticator in patients with esophageal squamous cell carcinoma receiving esophagectomy

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Background: Systemic inflammation response is a crucial prognostic factor for various cancers. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two inflammation-based prognostic scores. The significance of preoperative NLR and PLR in patients with esophageal squamous cell carcinoma (ESCC) receiving curative esophagectomy remains largely undefined. Hence, this study aimed to evaluate the significance of preoperative NLR and PLR in patients with ESCC receiving curative esophagectomy in southern Taiwan.

Methods: A consecutive group of 107 patients with ESCC undergoing esophagectomy between January 2001 and December 2012 were retrospectively reviewed. The NLR and PLR of these 107 patients were calculated and correlated with clinicopathological parameters, overall survival (OS), and disease-free survival (DFS).

Results: NLR ≥2.5 was significantly correlated with higher T classification (P=0.006) and advanced clinical AJCC 7th stage (P=0.047). PLR ≥150 was significantly associated with higher T classification (P=0.009). Univariate survival analysis showed that NLR ≥2.5 and PLR ≥150 were associated with poor OS (P=0.009 and P=0.007, respectively) and poor DFS (P=0.006 and P=0.005, respectively). On multivariate comparison, PLR ≥150 was independently associated with poor OS [P=0.001, hazard ratio (HR): 2.475] and poor DFS (P<0.001, HR: 2.509). The 5-year overall and DFS rates were, respectively, 33.3% and 25.0% in patients with PLR ≥150, and 54% and 46% in patients with PLR <150.

Conclusions: The PLR is an independent prognosticator for patients with ESCC undergoing esophagectomy in southern Taiwan.

Keywords: Esophageal cancer; squamous cell carcinoma; neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); esophagectomy

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Introduction

Globally, esophageal cancer was the seventh most common cancer and sixth most common cause of death in 2018 (1). In Taiwan, the major histology of esophageal cancer is squamous cell carcinoma, and esophageal cancer caused approximately 1,731 deaths in 2016. The 5-year survival of patients with esophageal cancer ranges from 15% to 20% (2). The prognosis of patients with esophageal squamous cell carcinoma (ESCC) remains poor even though radical surgery, chemotherapy, and radiotherapy have been performed since decades (3-5). Although patients with ESCC receive radical surgery and chemoradiotherapy, recurrence occurs (5). Hence, identifying easily available prognostic markers for ESCC is crucial for clinicians to prepare appropriate risk-adapted treatment plans.

Systemic inflammation is associated with the prognosis of various cancers (6). Indicators of systemic inflammatory response, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been investigated for their prognostic value in predicting the prognosis of various cancers (7,8). However, only a few studies have investigated the prognostic value of NLR and PLR for patients with esophageal cancer. Moreover, the significance of preoperative NLR and PLR in patients with ESCC receiving curative esophagectomy in southern Taiwan remains largely undefined. Therefore, we conducted a retrospective analysis to determine the significance of NLR and PLR in patients with ESCC undergoing curative esophagectomy in southern Taiwan.

Methods

Patient population

Patients with ESCC who underwent surgical resection at Kaohsiung Chang Gung Memorial Hospital between January 2001 and December 2012 were retrospectively evaluated. This retrospective study was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201901532B0). After excluding patients treated with preoperative chemoradiotherapy, those treated with preoperative chemotherapy or radiotherapy, those with synchronous cancers, and those lost to follow-up, 107 patients receiving esophagectomy were enrolled and analyzed. Radical esophagectomy (the McKeown procedure or Ivor Lewis procedure), reconstruction with gastric tube pull-up, and two-field lymph node dissection were performed. The pathological TNM stage was determined according to the 7th American Joint Committee on Cancer (AJCC) staging system. Follow-ups were performed every 3 months in years 1 and 2, every 6 months in years 3–5, and after 1 year thereafter. Overall survival (OS) was defined as the time of surgery to death from any cause. Disease-free survival (DFS) was calculated from the time of surgery to recurrence or death from any cause without evidence of recurrence.

NLR and PLR

The neutrophil count, lymphocyte count, and platelet count before esophagectomy were retrospectively recorded for the included 107 patients. The NLR was defined as the neutrophil count divided by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count; the cut-off values for the NLR and PLR were 2.5 and 150, respectively, according to previous studies (9,10).

Statistical analysis

Comparisons between groups were performed using the chi-square test and Fisher's exact test. Survival was calculated using the Kaplan-Meier method for univariate analysis, and the differences were assessed using the long-rank test. Multivariate analysis for significant parameters at the univariate level was performed using the Cox regression model in a stepwise forward fashion. Statistical significance was defined as $P<0.05$. All analyses were conducted using SPSS21.0 software package (IBM Corp. Released 2012. IBM SPSS Statistics for Window, Version 21.0. Armonk, NY, USA).

Results

Patient characteristics

A total of 107 patients were enrolled (104 men and 3 women), and the median age was 55 years (range, 29–80 years). The clinicopathological characteristics are shown in *Table 1*.

Table 2 shows the correlations between NLR and PLR, and the clinicopathological parameters. NLR ≥2.5 was significantly associated with the T classification T3+T4 (P=0.006), 7th AJCC stage III (P=0.047), positive surgical margin (P=0.039), and PLR ≥150 (P<0.001). PLR ≥150 was significantly correlated with the T classification T3+T4 (P=0.009).

Table 1 The general characteristics of 107 patients with esophageal squamous cell carcinoma receiving esophagectomy

Variables	N (%)
Age, years	Median: 55; mean: 56; range, 29–80
Sex	
Male	104 (97.2)
Female	3 (2.8)
Primary tumor location	
Upper	20 (18.7)
Middle	40 (37.4)
Lower	47 (43.9)
T classification	
T1	47 (43.9)
T2	25 (23.4)
T3	25 (23.4)
T4	10 (9.3)
N classification	
N0	71 (66.4)
N1	24 (22.4)
N2	10 (9.3)
N3	2 (1.9)
7th AJCC stage	
IA	5 (4.7)
IB	37 (34.6)
IIA	11 (10.3)
IIB	28 (26.2)
IIIA	11 (10.3)
IIIB	4 (3.7)
IIIC	11 (10.3)
Histological grading	
Grade 1	11 (10.3)
Grade 2	70 (65.4)
Grade 3	26 (24.3)
Surgical margin	
Negative	96 (89.7)
Positive	11 (10.3)
NLR	
NLR <2.5	51 (47.7)
NLR ≥2.5	56 (52.3)
PLR	
PLR <150	59 (55.1)
PLR ≥150	48 (44.9)

AJCC, American Joint Committee on Cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

Survival analyses

At the time of analysis, the median follow-up periods were 65 months (range, 60.4–112 months) for 52 survivors and 58 months (range, 1.3–112 months) for all 107 patients. The 5-year OS and DFS rates for these 107 patients were 49% and 40%, respectively.

Table 3 shows the correlations between the clinicopathological parameters, PLR, and NLR, and the OS and DFS. Univariate survival analyses found that the T classification T3+T4 (P=0.02), N classification N1+2+3 (P<0.001), 7th AJCC stage II+III (P=0.011), positive surgical margins (P=0.004), NLR ≥2.5 (P=0.009) and PLR ≥150 (P=0.007) were significantly associated with poor OS. The T classification T3+T4 (P=0.004), N classification N1+2+3 (P<0.001), 7th AJCC stage II+III (P=0.009), positive surgical margins (P=0.018), NLR ≥2.5 (P=0.006), and PLR ≥150 (P=0.005) were significantly associated with poor DFS.

The 5-year OS rates were 54.9% and 35.7% in patients with NLR <2.5 and NLR ≥2.5, respectively (P=0.009; *Figure 1A*), and the 5-year DFS rates were 47.1% and 26.8% (P=0.006; *Figure 1B*). The 5-year OS rate were 54.2% and 33.3% in patients with PLR <150 and PLR ≥150, respectively (P=0.007; *Figure 1C*) and the 5-year DFS rates were 45.8% and 25.0% (P=0.005; *Figure 1D*). *Table 4* shows the results of multivariate analysis. PLR ≥150 and lymph node classification N1+2+3 were significantly independently associated with poor OS [P=0.001, hazard ratio (HR): 2.475; 95% confidence interval (CI), 1.458–4.023; P<0.001, HR: 3.893; 95% CI, 2.268–6.683]. Additionally, independent factors for poor DFS were PLR ≥150 (P<0.001, HR: 2.509; 95% CI, 1.523–4.135) and lymph node classification

Table 2 Associations between NLR and PLR and the clinicopathological parameters in 107 patients with esophageal squamous cell carcinoma receiving esophagectomy

Parameters	NLR			PLR		
	<2.5	≥2.5	P value	<150	≥150	P value
Age, years						
<55	19	34	0.015*	27	26	0.387
≥55	32	22		32	22	
Primary tumor location						
U+M	29	31	0.875	34	26	0.720
L	22	25		25	22	
T classification						
T1+T2	41	31	0.006*	46	26	0.009*
T3+T4	10	25		13	22	
N classification						
N0	35	36	0.635	39	32	0.951
N1+2+3	16	20		20	16	
7th AJCC stage						
I	22	20	0.432	24	18	0.738
II+III	29	36		35	30	
7th AJCC stage						
I+II	43	38	0.047*	47	34	0.290
III	8	18		12	14	
Histological grading						
Grade 1+2	39	42	0.859	44	37	0.764
Grade 3	12	14		15	11	
Surgical margin						
Negative	49	47	0.039*	56	40	0.061
Positive	2	9		3	8	
PLR						
<150	49	10	<0.001*	-	-	-
≥150	2	46		-	-	-

*, statistically significant. AJCC, American Joint Committee on Cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

N1+2+3, (P<0.001, HR: 3.372; 95% CI, 2.014–5.646).

Discussion

Abundant evidence shows that systemic inflammation response is associated with tumor proliferation and progression (11,12) as well as cancer prognosis (7,8,10). Neutrophilia and thrombocytosis are caused by inflammatory responses resulting from cancer (13). Megakaryocytes are motivated by pro-inflammatory

Table 3 Results of univariate log-rank analysis of prognostic factors for overall survival and disease-free survival in 107 patients with esophageal squamous cell carcinoma receiving esophagectomy

Factors	No. of patients	Overall survival (OS)		Disease-free survival (DFS)	
		5-yr OS (%)	P value	5-yr DFS (%)	P value
Age, years					
<55	53	50.9	0.298	45.3	0.105
≥55	54	38.9		27.8	
Location					
U+M	60	50	0.196	38.3	0.373
L	47	38.3		34	
T classification					
T1+2	72	52.8	0.02*	41.3	0.004*
T3+4	35	28.6		25.7	
N classification					
N0	71	56.3	<0.001*	45.1	<0.001*
N1+2+3	36	22.2		19.4	
7th AJCC stage					
I	42	57.1	0.011*	49.6	0.009*
II+III	65	36.9		29.2	
7th AJCC stage					
I+II	81	53.1	<0.001*	42.0	<0.001*
III	26	19.2		19.2	
Histological grading					
Grade 1+2	81	45.7	0.574	35.8	0.955
Grade 3	26	42.3		38.5	
Surgical margin					
Negative	96	47.9	0.004*	38.5	0.018*
Positive	11	18.2		18.2	
NLR					
<2.5	51	54.9	0.009*	47.1	0.006*
≥2.5	56	35.7		26.8	
PLR					
<150	59	54.2	0.007*	45.8	0.005*
≥150	48	33.3		25.0	

*, statistically significant. AJCC, American Joint Committee on Cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

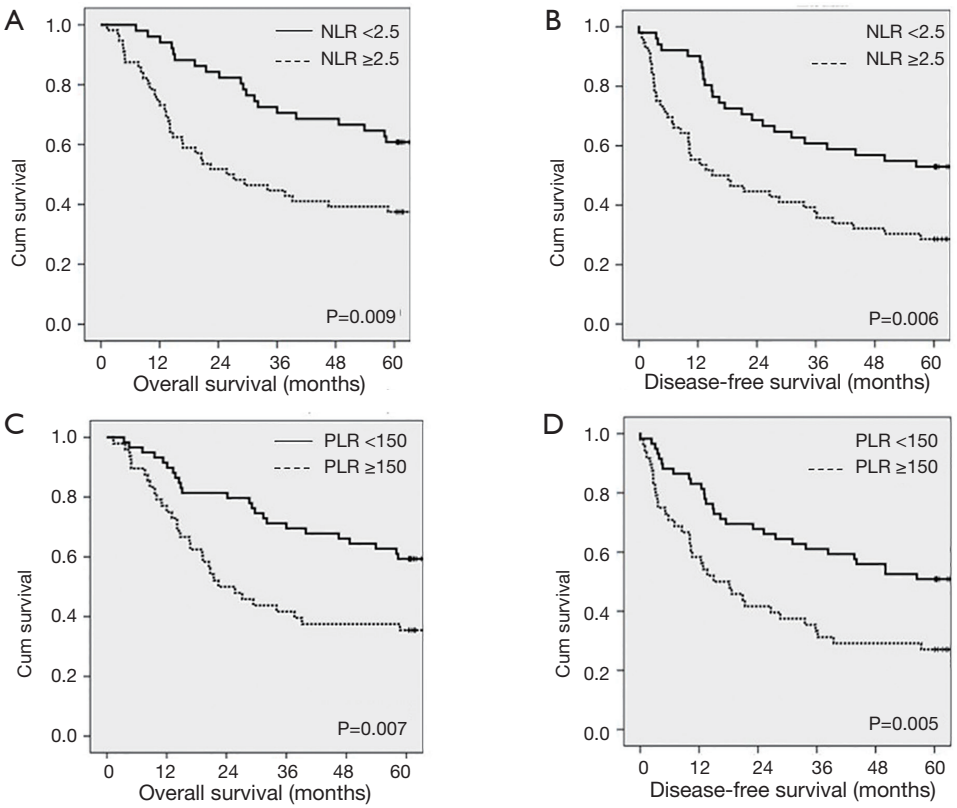

Figure 1 Kaplan-Meier curves according to the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). (A) Overall survival curve according to the NLR; (B) disease-free survival curve according to the NLR; (C) overall survival curve according to the PLR; (D) disease-free survival curve according to the PLR.

Table 4 Results of multivariate Cox regression analysis for overall survival and disease-free survival in 107 patients with esophageal squamous cell carcinoma receiving esophagectomy

Factors	Overall survival		Disease-free survival	
	OR (95% CI)	P value	OR (95% CI)	P value
Platelet lymphocyte ratio: PLR ≥150	2.475 (1.458–4.203)	0.001*	2.509 (1.523–4.135)	<0.001*
N classification: N1+2+3	3.893 (2.268–6.683)	<0.001*	3.372 (2.014–5.646)	<0.001*

*, statistically significant. OR, odds ratio; 95% CI, 95% confidence interval.

mediators such as interleukin (IL)-1, IL-2, and IL-6 caused by inflammation that results in a higher platelet count (9). NLR and PLR have been found to be prognostic factors in colorectal, gastric, lung, and ovarian cancers (14). However, whether preoperative PLR is a significant prognosticator in ESCC remains controversial. In previous studies, preoperative PLR was not an independent prognosticator for patients with esophageal cancer undergoing esophagectomy (15-18). In contrast, Xie *et al.* (19), Feng *et al.* (9), and Zhao *et al.* (6) demonstrated that preoperative PLR was an independent prognostic factor. These differences in results may be owing to the differences in the cut-off values of PLR, histology, treatment methods, and the definition of outcomes.

In our study, the cut-off value of NLR and PLR was 2.5 and 150, respectively. Both NLR ≥2.5 and PLR ≥150 were correlated with poor OS and DFS in 107 patients with ESCC receiving curative esophagectomy. However,

on multivariate analysis, only preoperative PLR was a significantly prognosticator.

Esophagectomy is one of the standard therapies for patients with ESCC, especially for patient with early stage disease. Extensive improvement in surgical techniques and perioperative monitoring has been achieved during the past decades. However, despite radical surgery, patients still develop recurrence and metastases, and the treatment outcomes were poor. Many studies (20,21) evaluating post-operative adjuvant therapy were performed to improve the inadequate survival rate achieved with esophagectomy alone. Therefore, it is important to recognize high-risk patients with tumor recurrence who may benefit from post-operative adjuvant therapy. In the present study, elevated PLR and NLR were highly representative of tumor aggressiveness and associated with poor DFS. The 5-year DFS rates were 26.8% and 47.1% in patients with NLR ≥2.5 and NLR <2.5, respectively. The 5-year DFS rates were 25% and 45.8% in patients with PLR ≥150 and PLR <150, respectively. These results indicate that elevated NLR and PLR may be helpful in the selection of some patients for post-operative adjuvant therapy. Furthermore, the PLR and NLR are easily measurable and available, and both are often regarded as routine preoperative tests in clinical practice.

This study has some limitations. The enrolled patient number was small and all the patients were from a single institution. Moreover, the study was retrospective, and may have had selection bias.

In conclusion, the results of our study suggest that PLR is an independent prognosticator for patients with ESCC undergoing esophagectomy and may be helpful in clinical practice.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201901532B0).

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