Original Article

Preoperative lymphocyte-monocyte ratio is not an independent prognostic factor in M0 (stage I–III) esophageal squamous cell carcinomas

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Background: Esophageal carcinoma is an invasive malignancy with a poor prognosis. Inflammatory cells are related to the prognosis in many malignancies; however, the prognostic values of preoperative neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) in esophageal squamous cell carcinomas (ESCCs) are contentious.

Methods: We performed a retrospective study on 178 patients who had proven ESCC and underwent R0 resection. A complete peripheral blood cell count on all patients 1 week before surgery was used to calculate NLR, LMR and PLR. All patients were grouped by the median count of NLR, LMR and PLR respectively. Kaplan-Meier curves were adopted to test the difference of overall survival (OS) and disease-free survival (DFS) between the high group of NLR, LMR and PLR and the low group. All data analysis was performed by SPSS. P<0.05 was assigned to admit statistical significance.

Results: The median follow-up after the surgery was 39 months. The preoperative LMR showed no significant association with the OS [hazard ratio (HR) =0.733, 95% confidence interval (CI): 0.397–1.353, P=0.321] and DFS (HR =0.850, 95% CI: 0.491–1.473, P=0.562). Neither NLR nor PLR exhibited a significant correlation with OS or DFS.

Conclusions: NLR, LMR, and PLR could not take the roles of prognostic biomarkers for patients with operable ESCCs.

Keywords: Esophageal squamous cell carcinomas (ESCCs); neutrophil-lymphocyte ratio (NLR); lymphocyte-monocyte ratio (LMR); platelets-lymphocyte ratio (PLR); prognostic biomarker

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Introduction

Esophageal cancer is the fourth most frequently diagnosed cancer in China (1). Esophageal squamous cell carcinoma (ESCC) represents over 90 percent of esophageal carcinoma in high-risk regions (2). Although there has been considerable progress in the development of treatments and therapeutic interventions, including chemotherapy, radiation, and surgery, the prognosis for ESCC patients is still poor due to the high incidence of local and metastatic recurrence (3). ESCC patients generally have a 5-year overall survival (OS) rate of below 28% (4) and the clinical variables commonly used for outcome prediction are not

precise. Therefore, the identification of novel prognostic markers may allow for improved risk stratification for patients with ESCC, which might contribute to the development of individualized treatment strategies.

Besides treatment- and patient-related factors, such as chemoradiotherapy and tumor stage, inflammation or innate immunity is causally related to the prognosis of cancers. Cancer-related inflammation plays a notable role in tumor development through inhibition of apoptosis, DNA damage, regulation of cytokines and inflammatory mediators, antitumor immunity and tumor angiogenesis (5). Inflammatory cells consist of a variety of leukocytes, including lymphocytes, neutrophils, macrophages, mast cells and dendritic cells. Recently, evidence has come to light indicating that inflammatory cells correlate with cancer prognosis in many malignancies. The neutrophil-lymphocyte ratio (NLR) in the circulation is an independent predictive factor for patients with renal cell carcinomas, gastric cancer, hepatocellular carcinomas and colorectal carcinomas (6). It has also been suggested that the peripheral PLR may be a prognostic marker in many malignancies (7). Nevertheless, the prognostic significance of the platelet-lymphocyte ratio (PLR) and NLR in ESCCs is contentious. Recently, the lymphocyte-monocyte ratio (LMR) was shown to be an inexpensive and easy prognostic marker to use in gastric cancer, pancreatic adenocarcinoma, colon cancer, soft tissue sarcoma, diffuse large B-cell lymphoma as well as classical Hodgkin's lymphoma (cHL) (8). To date, only two clinical research studies have suggested that LMR acts as a prognostic marker in ESCCs (9,10).

In this study, a retrospective analysis of 178 patients was performed to determine whether the preoperative LMR, NLR, and PLR could potentially be used as prognostic biomarkers for ESCCs.

Methods

Study patients

We performed this retrospective study on 178 patients who underwent esophagectomy between April 2006 and December 2012 at the Department of Thoracic Surgery, Tongji Hospital of Huazhong University of Science and Technology. Patients who had historically proven ESCC and underwent R0 resection were recruited. The exclusion criteria were as follows: neoadjuvant treatment, distal metastasis, and perioperative death. The medical records of all subjects were retrospectively reviewed and the clinicopathological information was collected. The tumor stage was determined in accordance with the standard in AJCC cancer staging manual (7th edition, 2010). Patients received postoperative follow-up every 4 months for the first 2 years and the follow-up interval was 6 months afterward. The last follow-up was in May 2015. Basic clinical information and the results from the physical examinations were collected at all visits. Computed tomography, barium meal fluoroscopy, and tumor marker assays were used.

LMR, NLR and PLR assessment

A complete peripheral blood cell count was performed on all patients 1 week before surgery. NLR = absolute neutrophil count/absolute lymphocyte count. LMR = absolute lymphocyte count/absolute monocyte count. PLR = total platelet count/total lymphocyte count.

Statistical analysis

The endpoints were the OS and the disease-free survival (DFS), both measured in months. OS is the time from the surgery to the last follow-up visit or the death of the patient (all causes). DFS is the period after the operation that the patient was tumor-free. Spearman's rank correlation coefficient was adopted in this study to analyze the relationships between NLR, PLR, and LMR. Pearson's chi-square test was performed here to assess the correlation between LMR/NLR/PLR and clinicopathological parameters, and NLR, PLR, and LMR were categorized into two groups using the median. Kaplan-Meier curves were used to evaluate OS and DFS. For the analysis of the prognostic parameters with known demographic and clinical prognostic factors, Univariate and multivariate analysis by Cox regression models were used. The enter method was used. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All data analysis was performed by SPSS (Version 16.0, SPSS Inc., Chicago, USA). $P<0.05$ was assigned to admit statistical significance.

Results

Patient characteristics

Of the 178 patients, there were 139 (78.1%) men and 39 (21.9%) women with a median age of 56 years (range, 38–76); 111 (62.4%) had smoked tobacco, 102 (57.3%) of patients had consumed alcohol, 34 (19.1%) were diagnosed

with stage III disease and 72 (40.4%) were treated with adjuvant therapy.

The overall median of the absolute white blood cell count was 5.68 (2.51–12.84) $\times 10^9$/L, 3.29 (0.7–7.11) $\times 10^9$/L for the absolute neutrophil count, 1.73 (0.74–4.21) $\times 10^9$/L for the absolute lymphocyte count, 0.43 (0.18–1.30) $\times 10^9$/L for the absolute monocyte count, and 203 (87–434) $\times 10^9$/L for the absolute platelet count.

LMR was negatively correlated with NLR (ρ=–0.578, P<0.001) and PLR (ρ=–0.513, P<0.001). NLR was positively correlated with PLR (ρ=0.528, P<0.001).

All ESCC patients were grouped by the median values of NLR, LMR, and PLR. Their clinical characteristics were shown (*Table 1*). We used the median count of NLR (1.89), PLR (118.91) and LMR (3.88) as cut-off values.

According to the median value of NLR, 91 patients were assigned to the high NLR group (≥1.89). The tumor length between patients with NLR <1.89 and those with NLR ≥1.89 was significantly different (P=0.038). No statistical significance was observed in these two groups regarding sex, age, alcohol consumption, tobacco smoking, tumor location, tumor stage, differential degree, and adjuvant therapy.

Eighty-nine patients were assigned in the high PLR group (≥118.91). There was no statistical significance in sex, age, tobacco smoking, alcohol consumption, tumor location, length, stage, differential degree and adjuvant therapy between the two groups.

According to the median value of LMR, eighty-nine patients were separated into the high LMR group (≥3.88), while the others were assigned in the low LMR group. Data showed a significant difference regarding sex (P=0.002), tobacco smoking (P=0.003) and alcohol consumption (P=0.015) between the groups. No statistical significance was found in age, tumor location, length, stage, differential degree and adjuvant therapy between the two groups.

Survival and prognostic value of NLR, PLR, and LMR in ESCC patients

The median follow-up was 39 months (range, 3–88 months). During this period, a total of 63 (35.4%) patients died and 75 (42.1%) patients had tumor recurrence. For all patients, the median DFS and OS were 37 and 39 months, respectively. The median DFS and OS of patients with tumor recurrence were 16 and 24 months, respectively.

Kaplan-Meier analysis showed lower but not significant OS (mean 39.1 *vs.* 43.8 months, P=0.087) and DFS (mean 35.1 *vs.* 40.4 months, P=0.115) in patients with high NLRs (*Figure 1*). Marginal reductions in OS (mean 40.6 *vs.* 42.2 months, P=0.330) and DFS (mean 36.3 *vs.* 39.1 months, P=0.259) were observed in the high versus low PLR group, but these differences were not significant. A worse but not significant prognosis was shown in patients with low preoperative LMR for OS (mean 40.1 *vs.* 42.6 months, P=0.187) and DFS (mean 36.8 *vs.* 38.6 months, P=0.400) compared with those with a high LMR.

As demonstrated in the univariate analysis, tumor length (P=0.037), tumor stage, (P=0.024; P<0.001) and adjuvant therapy (P<0.001) were significantly associated with the OS of patients (*Table 2*). By running multivariate analysis, we found that only tumor stage was independently associated with unfavorable OS (HR =1.943, 95% CI: 1.020–3.704, P=0.043; HR =3.374, 95% CI: 1.712–6.650, P<0.001, respectively). Neither NLR (HR =1.097, 95% CI: 0.598–2.010, P=0.765), PLR (HR =0.910, 95% CI: 0.511–1.622, P=0.749) nor LMR (HR =0.733, 95% CI: 0.397–1.353, P=0.321) were related to the OS of ESCCs.

Tumor length (P=0.046), tumor stage (P=0.031; P<0.001) and adjuvant therapy (P<0.001) were found to be significantly associated with DFS (*Table 3*). In multivariate analysis, only tumor stage was independently associated with unfavorable DFS (HR =1.734, 95% CI: 0.972–3.904, P=0.062; HR =3.467, 95% CI: 1.876–6.438, P<0.001, respectively). Similar analyses of NLR (HR =1.065, 95% CI: 0.620–1.828, P=0.820), PLR (HR =1.023, 95% CI: 0.607–1.726, P=0.932) and LMR (HR =0.850, 95% CI: 0.491–1.473, P=0.562) showed no associations with DFS.

Discussion

Since the first indication that chronic inflammation may cause many tumors about 150 years ago, it is widely recognized that inflammation and innate immunity are strongly associated with tumor development (11). In the current investigation, a retrospective study was performed on 178 ESCC patients who received a radical resection and the association between NLR/PLR/LMR with clinical outcome was assessed. This study is the first to show that LMR was not independently associated with DFS or OS in ESCC patients who had a radical resection. Furthermore, our data indicate that NLR and PLR are also not independently related to OS or DFS in ESCCs.

Contrary to prior research, we demonstrated that an elevated LMR was not significantly related to the increase

Table 1 Baseline characteristics of ESCC patients (n=178) stratified by NLR, PLR and LMR

Characteristic	Subgroup	Patients, n (%)	NLR, n			PLR, n			LMR, n		
			NLR <1.89 (n=87)	NLR ≥1.89 (n=91)	P value*	PLR <118.91 (n=89)	PLR ≥118.91 (n=89)	P value*	LMR <3.88 (n=89)	LMR ≥3.88 (n=89)	P value*
Gender	Male	139 (78.1)	65	74	0.287	68	71	0.587	78	61	0.002
	Female	39 (21.9)	22	17		21	18		11	28	
Age, years	<56	81 (45.5)	44	37	0.184	38	43	0.452	38	43	0.452
	≥56	97 (54.5)	43	54		51	46		51	46	
Tobacco smoking	Never	67 (37.6)	37	30	0.188	33	34	0.877	24	43	0.003
	Ever	111 (62.4)	50	61		56	55		65	46	
Alcohol drinking	Never	76 (42.7)	42	34	0.141	39	37	0.762	30	46	0.015
	Ever	102 (57.3)	45	57		50	52		59	43	
Tumor length, cm	≤3	80 (44.9)	46	34	0.038	43	37	0.366	40	40	1.000
	>3	98 (55.1)	41	57		46	52		49	49	
Tumor location	Upper	20 (11.2)	11	9	0.704	8	12	0.562	10	10	0.892
	Middle	73 (41.0)	37	36		39	34		35	38	
	Lower	85 (47.8)	39	46		42	43		44	41	
Differential degree	Well	103 (57.9)	49	54	0.919	55	48	0.541	51	52	0.760
	Middle	65 (36.5)	33	32		29	36		34	31	
	Poor	10 (5.6)	5	5		5	5		4	6	
Tumor stage	I	75 (42.1)	42	33	0.198	44	31	0.106	36	39	0.882
	II	69 (38.8)	32	37		32	37		36	33	
	III	34 (19.1)	13	21		13	21		17	17	
Adjuvant therapy	No	106 (59.6)	58	48	0.059	58	48	0.127	50	56	0.360
	Yes	72 (40.4)	29	43		31	41		39	33	

*, difference between groups was tested by Chi-square test. ESCC, esophageal squamous cell carcinoma; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.

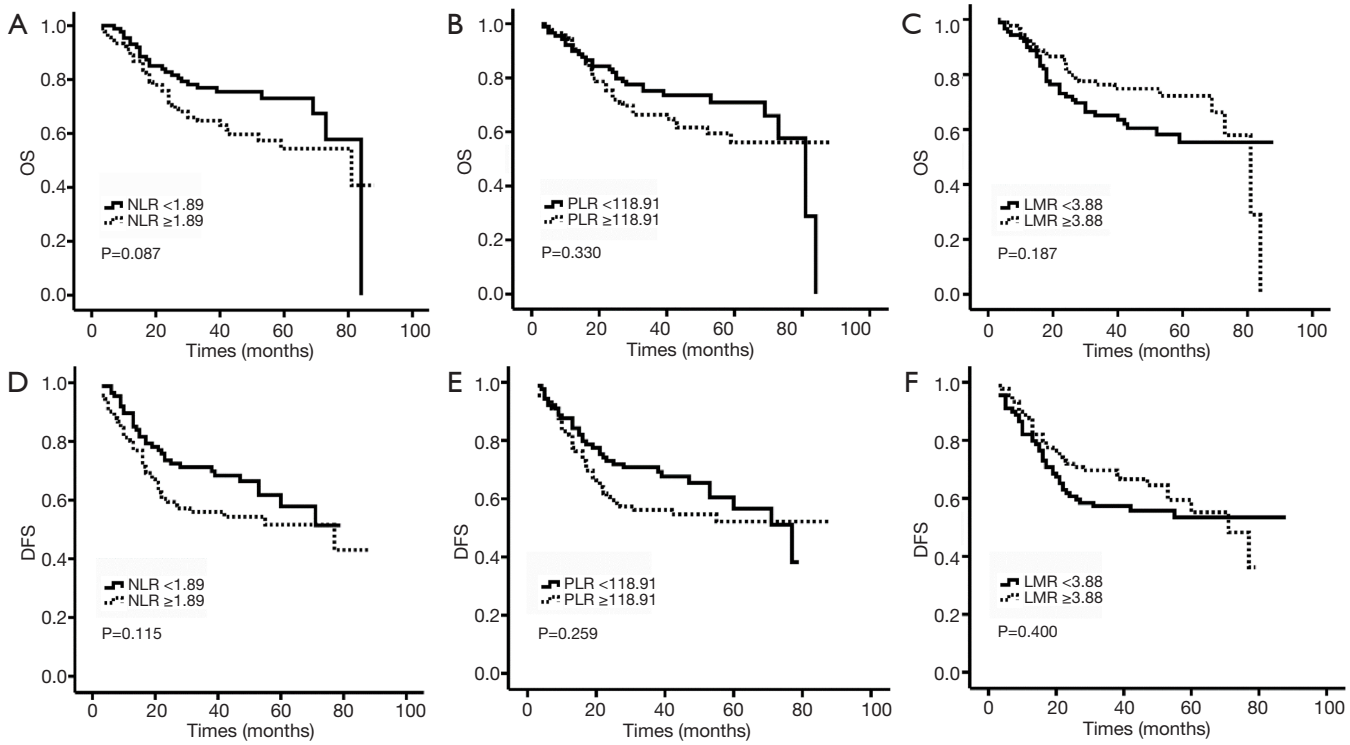

Figure 1 Prognostic value of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) in patients with esophageal squamous cell carcinoma (ESCC). Kaplan-Meier curves of the overall survival (OS) for all patients stratified by NLR (A), PLR (B) and LMR (C). Kaplan-Meier curves of the disease-free survival (DFS) for all patients stratified by NLR (D), PLR (E) and LMR (F).

in OS and DFS in operable ESCC patients. Huang *et al.* studied 348 patients who had undergone esophagectomy for ESCCs and showed that patients with LMR ≤2.93 had a significantly poorer 5-year cancer-specific survival (CSS) than those with LMR >2.93 (21.2% *vs.* 59.3%, P<0.001) (9). Han *et al.* analyzed 218 patients with ESCC who received radical surgery and showed that, for both OS and DFS, preoperative LMR was an independent prognostic factor (10).

We assessed the potential prognostic significance of PLR and NLR. Despite an inverse association between NLR/PLR and prognosis in various tumors, their roles in esophageal cancer are confusing. Feng *et al.* (12) showed that PLR and NLR acted as markers of OS in ESCCs, and Yoo *et al.* (13) and Sharaiha *et al.* (14) proposed that an increasing NLR was related to poor OS and DFS in esophageal cancer. Conversely, other studies found that the predictive value of preoperative NLR and/or PLR for CSS was low in esophageal cancer patients (15,16). In the current study, increased NLR or PLR did not prove to be an independent prognostic factor.

Our results differ from other studies with reasons likely to include the cut-off values of these ratios, different pathological types, treatment modality and population. No available cut-off value was found in our population by receiver operating characteristic (ROC) curves; thus, we used the median count of NLR, PLR, and LMR as cut-off values. Furthermore, we analyzed the prognostic role of NLR, PLR, and LMR in ESCC patients without neoadjuvant therapy as radiation and/or chemotherapy could have exerted important impacts on systemic inflammation. Therefore, only 19.1% of patients were diagnosed with stage III disease and 42.1% of patients developed tumor recurrence in the current study. Also, we excluded adjuvant therapy from the multivariant analysis as it was dependent on the tumor stage.

Despite the unclear mechanism, many studies have shown that inflammatory and immune cells are related to malignancy. However, it is a complicated process that takes

Table 2 Univariate and multivariate analysis of prognostic factors of overall survival by Cox regression model

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender (female)	0.613 (0.311–1.208)	0.158	–	–
Age (≥56 years)	0.922 (0.562–1.513)	0.748	–	–
Tobacco smoking (ever)	1.061 (0.633–1.779)	0.823	–	–
Alcohol drinking (ever)	1.135 (0.687–1.875)	0.622	–	–
Tumor length (>3 cm)	1.758 (1.036–2.984)	0.037	1.392 (0.800–2.420)	0.242
Tumor location				
Upper	1.000	–	–	–
Middle	1.925 (0.671–5.521)	0.223	–	–
Lower	2.257 (0.798–6.386)	0.125	–	–
Differential degree				
Well	1.000	–	–	–
Middle	1.154 (0.684–1.947)	0.590	–	–
Poor	0.992 (0.304–3.233)	0.989	–	–
Tumor stage				
I	1.000	–	1.000	–
II	2.070 (1.100–3.893)	0.024	1.943 (1.020–3.704)	0.043
III	3.770 (1.977–7.192)	<0.001	3.374 (1.712–6.650)	<0.001
Adjuvant therapy (yes)	3.425 (2.026–5.790)	<0.001	–	–
NLR ≥1.89	1.549 (0.933–2.572)	0.091	1.097 (0.598–2.010)	0.765
PLR ≥118.91	1.279 (0.777–2.105)	0.333	0.910 (0.511–1.622)	0.749
LMR ≥3.88	0.716 (0.434–1.182)	0.192	0.733 (0.397–1.353)	0.321

Note: adjuvant therapy was not included in the multivariable analysis, because it depends on the tumor stage. NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CI, confidence interval.

place in the tumor microenvironment (17-19). For example, myeloid growth factors (a production of paraneoplastic syndrome), granulocyte colony stimulating factor derived from cancer cells, and the release of interleukin-6 and tumor necrosis factor-α have also been attributed to neutrophilia in the malignant process. Moreover, unlike colorectal cancer, which is related to ulcerative colitis and esophageal adenocarcinomas that are associated with reflux esophagitis, ESCCs do not arise from chronic or acute inflammation. All of the aforementioned factors may explain the difference in results relating to the different cancers between our study and others.

In our study, the limitations include the single-center design, a relatively small sample size, and retrospective analysis. Also, our subjects were recruited from a single ethnic group (Han Chinese). All of these factors might have caused selection bias and limit sample representativeness. Our findings need to be confirmed in a large-scale multicenter study. Furthermore, median values of NLR, PLR, and LMR were used as cut-off levels, and variant cut-off values served for prognostic markers of ESCC were needed to conduct further analysis. Additional mechanistic studies will also need to be performed.

In conclusion, we demonstrate that LMR could not serve as a prognostic biomarker for patients with operable ESCCs. Moreover, our findings may support further studies to investigate the roles of inflammatory cells in the ESCC microenvironment.

Table 3 Univariate and multivariate analysis of prognostic factors of disease-free survival by Cox regression model

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender (female)	0.718 (0.401–1.284)	0.264	–	–
Age (≥56 years)	0.805 (0.511–1.267)	0.348	–	–
Tobacco smoking (ever)	1.142 (0.712–1.831)	0.583	–	–
Alcohol drinking (ever)	0.966 (0.612–1.524)	0.881	–	–
Tumor length (>3 cm)	1.618 (1.009–2.594)	0.046	1.284 (0.785–2.099)	0.320
Tumor location				
Upper	1.000	–	–	–
Middle	1.663 (0.696–3.977)	0.253	–	–
Lower	1.533 (0.645–3.641)	0.333	–	–
Differential degree				
Well	1.000	–	–	–
Middle	1.048 (0.646–1.700)	0.850	–	–
Poor	1.935 (0.821–4.563)	0.131	–	–
Tumor stage				
I	1.000	–	1.000	–
II	1.861 (1.058–3.276)	0.031	1.734 (0.972–3.094)	0.062
III	3.824 (2.132–6.859)	<0.001	3.467 (1.867–6.438)	<0.001
Adjuvant therapy (yes)	3.506 (2.183–5.632)	<0.001	–	–
NLR ≥1.89	1.438 (0.909–2.275)	0.120	1.065 (0.620–1.828)	0.820
PLR ≥118.91	1.296 (0.822–2.042)	0.264	1.023 (0.607–1.726)	0.932
LMR ≥3.88	0.824 (0.524–1.298)	0.405	0.850 (0.491–1.473)	0.562

Note: adjuvant therapy was not included in the multivariable analysis, because it depends on the tumor stage. NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CI, confidence interval.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.75). 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 study had been approved by the Ethics Committee of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-C20061325).

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