Original Article

Clinical and prognostic significance of preoperative lymphocyte-monocyte ratio, neutrophil-lymphocyte ratio and neutrophil-monocyte ratio on esophageal squamous cell carcinoma patients

Qi-Xin Shang[1#], Yu-Shang Yang[1#], Wei-Peng Hu[1], Yong Yuan[1], Yan He[2], Jing-Ying Zhao[2], Ai-Fang Ji[2], Long-Qi Chen[1]

[1]Department of Thoracic Surgery, West China Hospital of Sichuan University, Chengdu, China; [2]Central Laboratory, Heping Hospital Affiliated to Changzhi Medical University, Changzhi City, China

Contributions: (I) Conception and design: LQ Chen, QX Shang, YS Yang; (II) Administrative support: WP Hu, Y He; (III) Provision of study materials or patients: Y Yuan, QX Shang; (IV) Collection and assembly of data: YS Yang, JY Zhao; (V) Data analysis and interpretation: QX Shang, LQ Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Long-Qi Chen, MD, PhD. Department of Thoracic Surgery, West China Hospital of Sichuan University, No. 37, Guoxue Alley, Chengdu, China. Email: drchenlq@scu.edu.cn; Prof. Ai-Fang Ji, MD, PhD. Central Laboratory, Heping Hospital Affiliated to Changzhi Medical University, No. 161 Jiefang East Street, Changzhi City, China. Email: jiaifang2003099@163.com.

Background: The interaction between tumor cells and inflammatory cells has not been systematically investigated in esophageal squamous cell carcinoma (ESCC). The aim of the present study was to evaluate whether preoperative lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and neutrophil-monocyte ratio (NMR) could predict the prognosis of ESCC patients undergoing esophagectomy.

Methods: A total of 1,883 patients with histologically diagnosed ESCC who underwent radical esophagectomy from May 2005 to May 2015 were retrospectively reviewed. Besides clinicopathological factors, "Survminer" package in R® was applied to determine the optimal cut-off point for LMR, NLR and NMR. Meanwhile, we evaluated the prognostic value of LMR, NLR, and PLR using Kaplan-Meier curves and Cox regression models.

Results: The median follow-up was 28.77 months (range, 1.60–247.90 months). The optimal cut-off point of LMR, NLR and NMR is 3.83, 2.06 and 7.21, respectively. Kaplan-Meier survival analysis of patients with low preoperative LMR demonstrated a significant worse prognosis for 5-year OS (P<0.001) than those with high preoperative LMR. The high NLR cohort had lower 5-year OS (P<0.001). No significant difference with 5-year OS was found in NMR (P=0.405). On multivariate analysis, preoperative LMR (P=0.018; HR =0.786, 95% CI: 0.645, 0.959) and NLR (P=0.028; HR =1.247, 95% CI: 1.024, 1.519) were the independent prognostic factors in ESCC patients. Integrating LMR and NLR, we divided the ESCC patients in four groups according to their cut-off points and we found the patients in LMR ≥3.83 and NLR <2.06 group received the best prognosis while the prognosis of patients in LMR<3.83 and NLR ≥2.06 group was the worst. The difference was statistically significant.

Conclusions: Preoperative LMR and NLR better predicts cancer survival in patients with ESCC undergoing esophagectomy, especially under the circumstances of LMR ≥3.83 and NLR <2.06.

Keywords: Lymphocyte-monocyte ratio (LMR); neutrophil-lymphocyte ratio (NLR); neutrophil-monocyte ratio (NMR); esophageal squamous cell carcinoma (ESCC); prognosis

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Introduction

It's well known that esophageal cancer is one of the most malignant cancer all over the world and only 10–40% esophageal cancer patients will survive for more than 5 years postoperatively (1,2). Meanwhile, China is a high incidence area for esophageal squamous cell carcinoma (ESCC) with the morbidity of 90% (3,4). The 5-year overall survival rate of ESCC patients in stage IIA–III treated by surgical resection alone is from 20.6% to 34.0% (5,6), which is almost the same as the patients administrated with multimodality therapies including surgery, chemotherapy and radiotherapy (7). TNM stage and tumor differentiation were demonstrated as the independent prognostic factor of esophageal cancer in previous reports (8), however, the heterogeneity of prognosis also exists in patients with same stage. Some investigators showed that cancer-related inflammation leads to worse prognosis, and the inflammatory biomarkers play an important role (9). At the same time, the neutrophil-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) have been reported to be the independent prognostic factor correlated to breast, gastric and lung cancer (10-12) previously, however, few studies have showed the prognostic role of the inflammatory biomarkers in ESCC, especially the role of neutrophil-monocyte ratio (NMR). What's more, the methods of optimal cut-off value determination in published esophageal cancer studies were various, some were empirical, therefore, we took the more practical and precise method to determine the optimal cut-off value of LMR, NLR and NMR in order to evaluate whether preoperative LMR, NLR and NMR plays a key role in survival of ESCC patients. We present this article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-2777).

Methods

Patients

A total of 1,883 patients with esophageal cancer who had accepted the radical esophagectomy at the Department of Thoracic Surgery, West China Hospital of Sichuan University from May 2005 to May 2015 were retrospectively reviewed. The exclusion criteria as follows: (I) patients who were lost to follow-up; (II) pathologically confirmed other types of thoracic esophageal cancer except for ESCC; (III) palliative surgery and R1 or R2 resection; (IV) patients with the total removed lymph nodes less than 10 (13); (V) patients who had accepted the preoperative or postoperative neoadjuvant chemotherapy or radiotherapy; (VI) tumor located less than 20cm from incisors; (VII) patients were accompanied with other malignant tumors. The study was approved by the human participants committee of West China Hospital of Sichuan University (the ethical number: 2005-126), and all patients were informed the risk of the operation. The use of their resected specimens and the written consents were obtained preoperatively. Among them, the median follow-up time is 28.77 months with the range from 1.60 to 167.90 months.

Blood sample analysis

Blood samples of hospitalized patients were adopted within 1 week before the surgery, anticoagulated by EDTA-K2 and examined by CELL DYN 1700 automatic hematologic analyzer (Abbott, USA) for blood routine. The complete blood cell (CBC) counts were extracted from the patents' medical records retrospectively and only the absolute counts of lymphocyte, monocyte and neutrophil were obtained from CBC data.

LMR, NLR and NMR calculation

The LMR was calculated by dividing the absolute lymphocyte count by absolute monocyte count. The NLR was calculated by dividing the number of absolute neutrophils by the number of absolute lymphocytes. Similarly, absolute neutrophil counts divided by the absolute monocyte counts is NMR. "Survminer" package in R® Version 3.4.0 (http://www.r-project.org/) was applied to determine the optimal cut-off point of LMR, NLR and NMR, which can provide a value of a cut-off point that correspond to the most significant relation with survival. The optimal cut-off point of LMR, NLR and NMR is 3.83, 2.06 and 7.21, respectively (*Figure 1A*,*B*,*C*).

Follow up

In our study, patients should be followed up every 3 months for the first and second year, every 6 months for the third to fifth year after the treatment, and finally the follow up will be transformed as every year after the fifth year. Blood routine, gastroscopy, chest CT, neck and abdominal ultrasound, when necessary, according to the patient's symptoms and physical examination. The tumor status (including tumor metastasis and recurrence), patients'

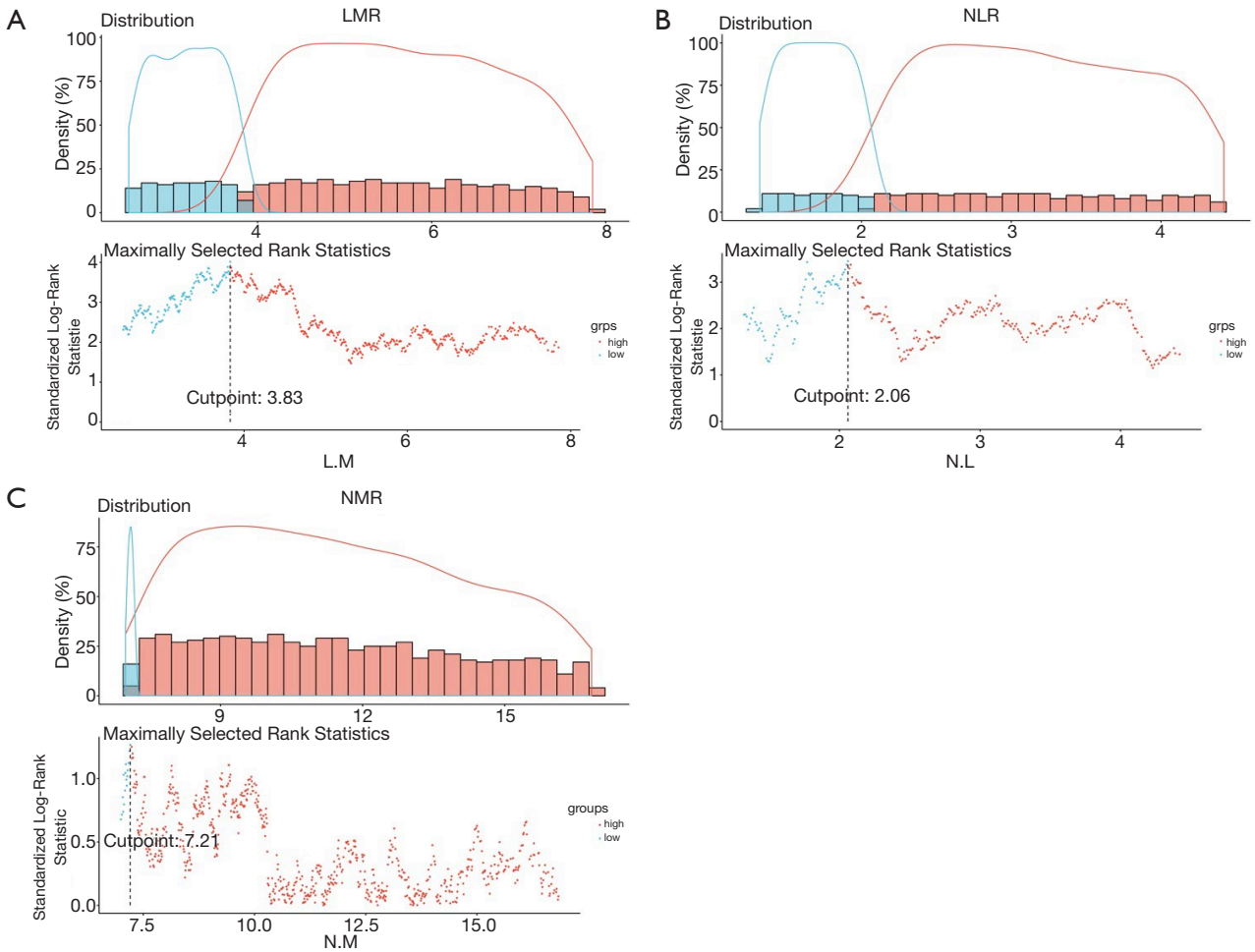

Figure 1 The optimal cut-off point value of lymphocyte-monocyte ratio (LMR), neutrophil-monocyte ratio (NLR) and neutrophil-monocyte ratio (NMR) calculated through "Survminer" package in R® Version 3.4.0 and the highest peak point is the optimal cut-off value of each category. (A) The optimal cut-off point of LMR is 3.83; (B) the optimal cut-off point of NLR is 2.06; (C) the optimal cut-off point of NMR is 7.21.

status (including survive and death) as well as the patients who were lost to follow up were all documented not only through outpatient follow up but also through telephone follow up and letter follow up.

Statistical analysis

The clinicopathologic features for each category (LMR, NMR and NLR) were showed in *Table 1*. In each category, the included patients were divided into two separated groups with regard to the optimal cut-off point. The logistic regression analysis was performed to determine the independent factors related to each category. The overall survival of each category was exhibited from the Kaplan-Meier curves and the log-rank test was used to determine the statistical significance. Multivariate survival analysis was figured out through the Cox proportional hazard regression model. The statistical significance was regarded as the probability value <0.05, and all the statistical analysis were conduct by IBM® SPSS® Statistics Version 21.0.

Results

All patients

A total of 1,883 ESCC patients who met the inclusion criteria were finally enrolled in our study. The median (range) age of the enrolled patients was 60 (range,

Table 1 The characteristics of 1,883 ESCC patients grouped by LMR, NLR and NMR

Characteristics	LMR			NMR			NLR		
	<3.83 [620]	≥3.83 [1,263]	P value	<7.21 [221]	≥7.21 [1,662]	P value	<2.06 [794]	≥2.06 [1,089]	P value
Gender			<0.001			0.196			<0.001
Male	566	984		187	1,363		599	951	
Female	149	279		34	299		195	138	
Age			0.148			0.163			0.177
<55	149	275		56	368		170	254	
≥55	471	988		165	1,294		624	835	
Surgical approach			0.651			0.106			0.288
Open	593	1,196		210	1,579		747	1,042	
Minimally	8	18		6	20		13	13	
Hybrid	19	49		5	63		34	34	
T stage			<0.001			0.577			<0.001
T1	69	236		29	276		165	140	
T2	83	241		40	284		163	161	
T3	328	599		110	817		352	575	
T4	140	187		42	285		114	213	
N stage			0.016			0.905			0.105
N0	311	703		115	899		447	567	
N1	167	327		58	436		199	295	
N2	109	173		36	246		101	181	
N3	33	60		12	81		47	46	
M stage			0.014			0.577			0.045
M0	610	1,257		219	1,648		791	1076	
M1	10	6		2	14		3	13	
Differentiation			0.040			0.127			0.520
High	86	190		23	253		125	151	
Moderate	360	786		137	1,009		476	670	
Low	174	287		61	400		193	268	
Location			0.014			0.879			0.520
Upper	61	123		20	164		73	111	
Middle	340	775		134	981		485	630	
Lower	219	365		67	517		236	348	
Vascular invasion			0.477			0.523			0.413
No	590	1,204		211	1,583		758	1,036	
Yes	30	59		10	79		36	53	

Table 1 (*continued*)

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Characteristics	LMR			NMR			NLR		
	<3.83 [620]	≥3.83 [1,263]	P value	<7.21 [221]	≥7.21 [1,662]	P value	<2.06 [794]	≥2.06 [1,089]	P value
TNM stage			<0.001			0.737			<0.001
I	64	212		27	249		143	133	
II	221	494		88	627		316	399	
III	325	551		104	772		332	544	
IV	10	6		2	14		3	13	
Recurrence			0.011			0.109			0.004
No	442	964		157	1,249		618	788	
Yes	178	299		64	413		176	301	

ESCC, esophageal squamous cell carcinoma; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; NMR, neutrophil-monocyte ratio; T stage, tumor stage; N stage, node stage; M stage, metastasis stage; TNM stage, tumor node metastasis stage.

20–92) years while the median survival time was 17.20 (range, 0.03–77.80) months. The clinicopathological features of all enrolled patients are presented in *Table 1*.

Clinical correlation of LMR, NMR and NLR

LMR

All patients were divided into two groups (LMR<3.83 and LMR ≥3.83) according to the cut-off point of LMR, in which 620 patients was in LMR<3.83 group while 1263 patients were classified into LMR ≥3.83 group. The clinicopathological characters of patients in LMR category were exhibited in *Table 1*. Gender (P<0.001) and T stage (P<0.001) showed significant differences among all the enrolled patients in LMR category through the univariate analysis of logistic regression. Meanwhile, the results of multivariate analysis in logistic regression showed that Gender (P<0.001 ; OR =2.735, 95% CI: 1.999, 3.743) and T stage (P<0.001; OR =0.721, 95% CI: 0.605, 0.858) were the independent factors correlated to enrolled ESCC patients in LMR category as well (*Table 2*).

NMR

According to the cut-off point of 7.21 in NMR, all patients were divided into two groups as well with 221 patients in NMR<7.21 group and 1,662 patients in NMR≥7.21 group. The clinicopathological features of patients in NMR category were showed in *Table 1* and none of the clinical features were significantly associated with NMR (*Table 2*).

NLR

Seven hundred ninety four patients were classified into the group of NLR <2.06 and the *Table 1* also listed the clinicopathological characters of patients in NLR category. From the univariate analysis of logistic regression, Gender (P<0.001) and T stage (P<0.001) showed significant differences among all the enrolled patients in NLR category, at the same time, Gender (P<0.001; OR =0.478, 95% CI: 0.374, 0.610) and T stage (P<0.001; OR=1.333, 95% CI: 1.147, 1.549) were demonstrated as the independent factors associated with NLR through the multivariate analysis of logistic regression (*Table 2*).

Prognostic value of LMR, NMR and NLR

In LMR category, the Kaplan-Meier curves showed that patients with low LMR had a worse overall survival (OS) (P<0.001, *Figure 2A*) when compared with high LMR group. Nevertheless, patients with low NLR had a better 5-year OS when compared with low NLR group (P<0.001, *Figure 2B*). No significant prognosis was found between the high NMR and low NMR group (P=0.210, *Figure 2C*), while the 5-year OS rate of patients with high NMR tended to be higher than that of the patients with low NMR.

In the univariate analysis of Cox proportional hazard regression, we found the T stage (P<0.001), N stage (P<0.001), vascular invasion (P=0.017), TNM stage (P<0.001), recurrence (P<0.001), LMR (P<0.001) and NLR (P<0.001) were significantly associated with 5-year OS (*Table 3*), while no significant difference with 5-year OS was found in NMR (P=0.405). Finally, LMR (P=0.018;

Table 2 Univariate and multivariate logistic regression analyses of 1,883 ESCC patients grouped by LMR, NLR and NMR

Variable	LMR				NMR				NLR			
	Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses	
	P	OR, 95% CI	P	OR, 95% CI	P	OR, 95% CI	P	OR, 95% CI	P	OR, 95% CI	P	OR, 95% CI
Gender	0.000	2.972 (2.181, 4.049)	0.000	2.735 (1.999, 3.743)	0.341	1.207 (0.820, 1.775)	–	–	0.000	0.446 (0.350, 0.567)	0.000	0.478 (0.374, 0.610)
Age	0.270	1.137 (0.905, 1.427)	–	–	0.286	1.193 (0.863, 1.651)	–	–	0.326	0.896 (0.719, 1.116)	–	–
Surgical approach	0.355	1.129 (0.873, 1.462)	–	–	0.579	1.117 (0.756, 1.649)	–	–	0.129	0.835 (0.662, 1.054)	–	–
T stage	0.000	0.715 (0.642, 0.796)	0.000	0.721 (0.605, 0.858)	0.248	0.915 (0.786, 1.064)	–	–	0.000	1.353 (1.227, 1.493)	0.000	1.333 (1.147, 1.549)
N stage	0.017	0.879 (0.791, 0.977)	0.649	0.965 (0.828, 1.125)	0.468	0.945 (0.810, 1.102)	–	–	0.257	1.061 (0.958, 1.176)	–	–
M stage	0.017	0.291 (0.105, 0.805)	0.054	0.337 (0.111, 1.019)	0.924	0.930 (0.210, 4.120)	–	–	0.071	3.186 (0.905, 1.216)	–	–
Differentiation	0.032	0.843 (0.721, 0.985)	0.177	0.892 (0.756, 1.053)	0.059	0.803 (0.638, 1.009)	–	–	0.450	1.059 (0.913, 1.228)	–	–
Location	0.032	0.839 (0.715, 0.985)	0.406	0.932 (0.790, 1.100)	0.995	0.999 (0.792, 1.261)	–	–	0.661	1.035 (0.889, 1.204)	–	–
Vascular invasion	0.872	0.964 (0.614, 1.512)	–	–	0.881	1.053 (0.537, 2.065)	–	–	0.737	1.077 (0.698, 1.662)	–	–
TNM stage	0.000	0.712 (0.622, 0.816)	0.403	1.130 (0.849, 1.503)	0.519	0.938 (0.773, 1.139)	–	–	0.000	1.342 (1.184, 1.522)	0.637	0.954 (0.786, 1.159)
Recurrence	0.018	0.770 (0.620, 0.957)	0.186	0.858 (0.684, 1.077)	0.188	0.811 (0.594, 1.107)	–	–	0.007	1.341 (1.083, 1.661)	0.062	1.234 (0.990, 1.539)

ESCC, esophageal squamous cell carcinoma; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; NMR, neutrophil-monocyte ratio; T stage, tumor stage; N stage, node stage; M stage, metastasis stage; TNM stage, tumor node metastasis stage; OR, odds ratio; 95% CI, 95% confidence interval.

HR =0.786, 95% CI: 0.645, 0.959), NLR (P=0.028; HR =1.247, 95% CI: 1.024, 1.519) as well as T stage (P<0.001; HR =1.464, 95% CI: 1.321, 1.622), N stage (P<0.001; HR =1.206, 95% CI: 1.094, 1.330), vascular invasion (P=0.018; HR =1.552, 95% CI: 1.079, 2.234), TNM stage (P<0.001; HR =1.878, 95% CI: 1.644, 2.145) and Recurrence (P<0.001; HR =3.212, 95% CI: 2.676, 3.855) were drawn as the independent prognostic factors for ESCC patients from the multivariate analysis of Cox proportional hazard regression.

The prognostic relationship among LMR, NLR and ESCC

Now that there's no significant difference of survival in patients of NMR category meanwhile, it was not demonstrated as the independent prognostic factor for ESCC patients, therefore, NMR was excluded from the research of the prognostic relationship between the inflammatory factor and ESCC. We integrated the role of LMR and NLR in prognosis of ESCC patients and the enrolled patients were divided into four groups according to their cut-off points: LMR <3.83 and NLR <2.06 group, LMR <3.83 and NLR ≥2.06 group, LMR ≥3.83 and NLR <2.06 group as well as LMR ≥3.83 and NLR ≥2.06 group. 66, 554, 728 and 535 patients were in the above groups respectively. The Kaplan-Meier curves showed that patients with both LMR and NLR less or greater than their cut-off points got almost the same survival. Patients in LMR ≥3.83 and NLR <2.06 group had the significant better prognosis when compared with patients in LMR ≥3.83 and NLR ≥2.06 group (P=0.041, *Figure 3*) and patients in LMR<3.83 and NLR ≥2.06 group (P<0.001). At the same time, patients in LMR <3.83 and NLR ≥2.06 group had a worse overall survival compared with patients in LMR ≥3.83 and NLR ≥2.06 group (P=0.022, *Figure 3*). No significant prognosis was found among patients in LMR<3.83 and NLR <2.06 group and patients in other groups. In the univariate analysis of Cox proportional hazard regression, the group was significantly associated with OS (P=0.030; HR =0.912, 95% CI: 0.839, 0.991), while, it was not recognized as the independent prognostic factor for ESCC patients through multivariate analysis.

Discussion

To our knowledge, the inflammatory factors such as C-reactive protein (CRP) levels, neutrophil, lymphocyte, monocyte and platelet counts in blood may play the prognostic role on various cancers and several studies have

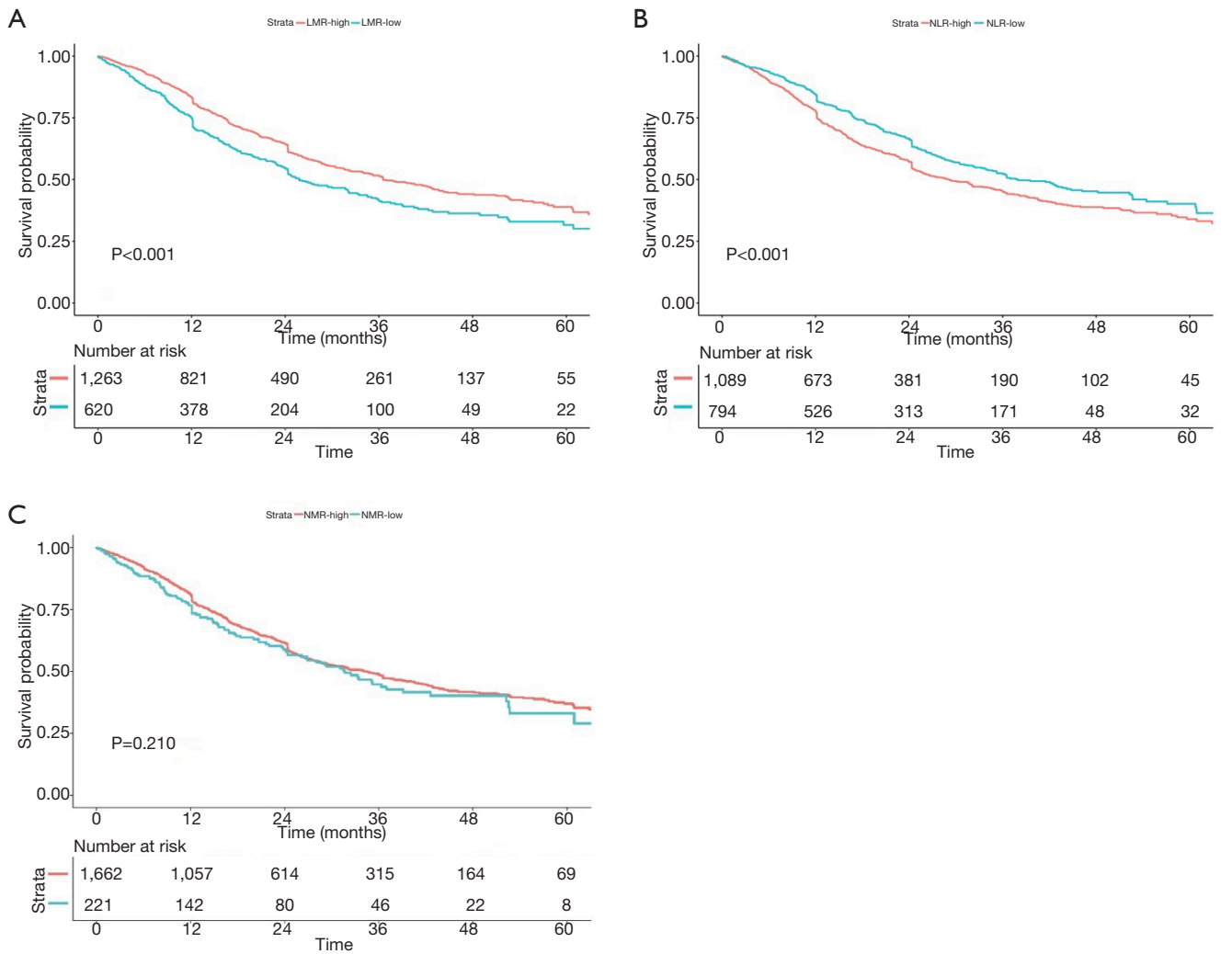

Figure 2 Kaplan-Meier survival curves of overall survival in 1,883 patients with esophageal squamous cell carcinoma classified into 2 group according to lymphocyte-monocyte ratio (LMR), neutrophil-monocyte ratio (NLR) and neutrophil-monocyte ratio (NMR). (A) Patients with low LMR had a worse overall survival when compared with high LMR group (P<0.001); (B) patients with low NLR had a better overall survival when compared with low NLR group (P<0.001); (C) no significant prognosis was found between the high NMR and low NMR group (P=0.210).

reported that the NLR, LMR and PLR were associated with the prognosis with ESCC (14-16). However, neither were the results of these studies consistent, nor were they conclusive, especially for the results of LMR. And there's even no study about the role of NMR in prognosis of ESCC but in breast cancer (17). Some of the scholars put neoadjuvant or/and adjuvant into their researches, however, neoadjuvant or/and adjuvant therapy has been confirmed as the independent prognostic factor of ESCC (18,19), meanwhile, chemotherapy agents also have been proved to modulated the immune response of cancer (20), which, to a degree, did reflect the prognostic of the inflammatory factors in ESCC authentically (21-23). Furthermore, the methods for determining optimal cut-off value of these inflammatory ratios in different studies were various, some chose the median value of the ratio (22,24), while others picked the Receiver operating characteristics (ROC) curve analysis for the optimal cut-off value determination (16,17,23,25). Therefore, we conducted the retrospective study not only for determining the optimal cut-off values of LMR, NLR and NMR by means of R®, but also for systematically finding out the impact of LMR, NLR and

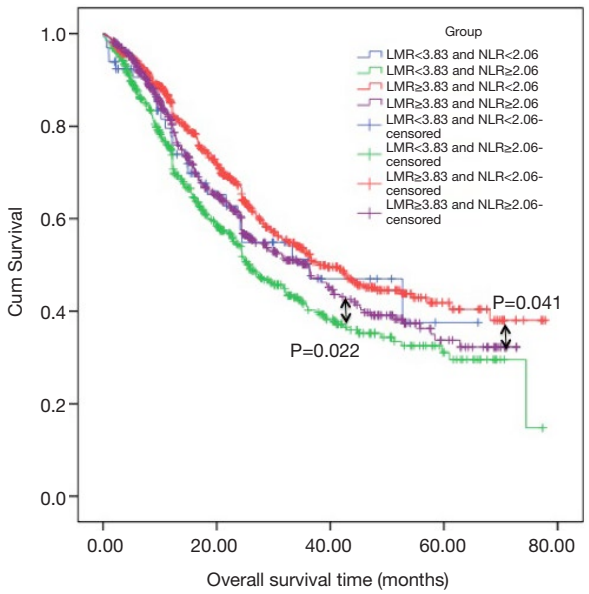

Figure 3 Kaplan-Meier survival curves by integrating the role of lymphocyte-monocyte ratio (LMR) and neutrophil-monocyte ratio (NLR) in prognosis of esophageal squamous cell carcinoma patients. Patients with both LMR and NLR less or greater than their cut-off points got almost the same survival. Patients in LMR ≥3.83 and NLR <2.06 group had the significant better prognosis when compared with patients in LMR ≥3.83 and NLR ≥2.06 group (P=0.041) and patients in LMR <3.83 and NLR ≥2.06 group (P<0.001). Patients in LMR <3.83 and NLR ≥2.06 group had a worse overall survival compared with patients in LMR ≥3.83 and NLR ≥2.06 group (P=0.022). No significant prognosis was found among patients in LMR<3.83 and NLR <2.06 group and patients in other groups.

NMR on ESCC patients without receiving adjuvant therapy pre-or postoperatively.

In present study, 1,883 ESCC patients were finally enrolled. Both Gender and T stage were demonstrated as the independent factor correlated to LMR and NLR except for NMR. What's more, more male patients were found to be associated with high NLR (P<0.001; OR =0.478, 95% CI: 0.374, 0.610) and low LMR (P<0.001; OR =2.735, 95% CI: 1.999, 3.743). Meanwhile, the deeper of the depth of tumor invasion (T stage), the higher NLR (P<0.001; OR =1.333, 95% CI: 1.147, 1.549) as well as the lower LMR (P<0.001; OR =0.721, 95% CI: 0.605, 0.858) were detected. Sun *et al.* (26) reviewed twenty-six studies including 8,586 ESCC patients for analyzing the clinical use of NLR, PLR and LMR, and the results were calculated as same as ours with high NLR was associated with gender (P=0.002; OR =1.58, 95% CI: 1.19, 2.10) and T stage (P<0.001; OR =1.95, 95% CI: 1.46, 2.60) and low LMR was relevant to gender (P=0.049; OR =0.61, 95% CI: 0.37, 1.00) and T stage (P<0.001; OR =0.58, 95% CI: 0.48, 0.69). With the deeper infiltration of esophageal cancer, the symptoms of esophageal obstruction will get worse and worse. Aspiration pneumonia, cachexia and electrolyte disorders are considered to be the manifestation of advanced esophageal cancer, especially for aspiration pneumonia. And fevers, weight and malnutrition may all be attributed to tumor-induced inflammation (27). Meanwhile, neutrophils are the main inflammatory cells that participate in the tumor microenvironment and promote tumor proliferation, metastasis and invasion (28-31). The main component of human anti-tumor immunity is lymphocytes. Studies have confirmed that the reduction of lymphocytes in tumor stroma will benefit for tumor proliferation and metastasis, leading to the poor prognosis consequently (32). No clinicopathological characters of ESCC patients were significantly correlated to NMR, and Losada *et al.* (17) have once analyzed the role of pretreatment NMR in 113 breast cancer patients, and no significant differences among patient characters were found in NMR category as well, which was the same result as we did.

As for the prognosis of LMR, in our study we found the low LMR was correlated to worse 5-year OS in ESCC patients. Actually, the mechanism between them is still unclear. However, the increasing investigation has indicated that the inflammatory factors contribute to tumor development, progression and metastasis, especially for NLR and LMR (33). Lymphocytes were reported to be critical in cell-mediated antitumor immune response (34). The CD8+T cell was infiltrated and activated by CD4+T cell, which induce apoptosis of tumor cells and have cytotoxic activity against cancer cells (35). What's more, tumor cells may escape from host immune surveillance attribute to the inhibition of lymphocytes cytotoxic response initiated by the tumor-related systemic inflammation. Finally, the tumor cell proliferation and migration were suppressed as well as the micrometastases or residual tumor cell were eliminated (36). Furthermore, it's reported that the lymphocyte counts were low in some cancers, which contributed to the inadequate immune response, leading to the lower survival subsequently (37).

In terms of monocytes, it's reported that tumor-associated macrophages (TAMs) were a primary part of the mononuclear leukocyte population in human solid tumors (38), originating form circulating monocytes, which played a central role in tumor angiogenesis, invasion,

Table 3 Univariate and multivariate analyses of prognostic factors in ESCC

Variable	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	P	HR (95% CI)
Gender	0.019	0.755, (0.597, 0.955)	0.221	0.860 (0.675, 1.095)
Age	0.024	1.311 (1.037, 1.658)	0.082	1.236 (0.973, 1.568)
Surgical approach	0.840	0.977 (0.780, 1.224)		
Open		Ref		
Minimally	0.507	1.250 (0.646, 2.418)		
Hybrid	0.684	0.904 (0.558, 1.467)		
T stage	0.000	1.681 (1.529, 1.849)	0.000	1.464 (1.321, 1.622)
T1		Ref		Ref
T2	0.000	1.998 (1.386, 2.880)	0.006	1.685 (1.165, 2.436)
T3	0.000	3.323 (2.429, 4.547)	0.000	2.347 (1.694, 3.252)
T4	0.000	5.073 (3.632, 7.084)	0.000	3.257 (2.289, 4.635)
N stage	0.000	1.529 (1.458, 1.738)	0.000	1.206 (1.094, 1.330)
N0		Ref		Ref
N1	0.000	2.017 (1.645, 2.473)	0.004	1.362 (1.101, 1.685)
N2	0.000	2.756 (2.183, 3.479)	0.000	1.571 (1.228, 2.009)
N3	0.000	3.356 (2.315, 4.865)	0.032	1.531 (1.037, 2.262)
M stage	0.003	3.451 (1.537, 7.751)	0.669	1.196 (0.526, 2.721)
Differentiation	0.000	1.285 (1.122, 1.471)	0.422	1.063 (0.916, 1.232)
High		Ref		Ref
Moderate	0.011	1.408 (1.083, 1.830)	0.782	0.968 (0.722, 1.215)
Low	0.000	1.706 (1.279, 2.277)	0.212	1.170 (0.914, 1.499)
Location	0.874	0.988 (0.852, 1.145)		
Upper		Ref		
Middle	0.573	0.913 (0.666, 1.252)		
Lower	0.680	0.932 (0.669, 1.300)		
Vascular invasion	0.017	1.548 (1.082, 2.214)	0.018	1.552 (1.079, 2.234)
TNM stage	0.000	2.219 (1.944, 2.532)	0.000	1.878 (1.644, 2.145)
I		Ref		Ref
II	0.000	1.827 (1.318, 2.533)	0.002	1.692 (1.220, 2.347)
III	0.000	4.343 (3.183, 5.926)	0.000	3.343 (2.440, 4.580)
IV	0.000	11.909 (5.588, 25.380)	0.000	5.910 (2.749, 12.707)
Recurrence	0.000	3.919 (3.287, 4.672)	0.000	3.212 (2.676, 3.855)
LMR	0.000	0.709 (0.549, 0.846)	0.018	0.786 (0.645, 0.959)
NMR	0.405	0.897 (0.696, 1.158)		
NLR	0.000	1.382 (1.159, 1.649)	0.028	1.247 (1.024, 1.519)

ESCC, esophageal squamous cell carcinoma; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; NMR, neutrophil-monocyte ratio; T stage, tumor stage; N stage, node stage; M stage, metastasis stage; TNM stage, tumor node metastasis stage; HR, hazard ratio; 95% CI, 95% confidence interval; Ref, reference.

migration, metastasis and inhibition of autoimmune response towards tumor cells (39,40). Some studies have reported the TAM count had a positive correlation with the peripheral blood macrophage percentage and would lead a worse prognosis in multiple cancers if the TAM presented a high infiltration (41). Therefore, not only can circulating monocytes take the place of TAMs in peripheral blood to reflect tumor burden but also it combined with lymphocytes may be considered as a potential, representative biomarker of host immunity versus tumor microenvironment.

Neutrophils, which proliferate and differentiate in bone marrow, is activated by some inflammatory mediators such as granulocyte and granulocyte-macrophage colony stimulating factors (42). The mature neutrophils in human systemic inflammation have been identified as a unique circulating population of myeloid cells (28). Some researches demonstrated that not only did neutrophils produce the factors, which participant in tumor angiogenesis, invasion, migration and metastasis, but also it is capable of inhibiting T cell responses (28-30). Finally, tumor progression decreases with the suppression of neutrophil infiltration. In our study, elevated NLR was associated with worse 5-year OS in ESCC patients, which confirmed the role of neutrophils in tumor patients on the one hand. On the other hand, several studies got the same results as we did (15,16,21-23). However, no significant prognosis was found between the high NMR and low NMR group nor was NMR found to be the independent prognostic factor of ESCC. The results of Kaplan-Meier analysis of NMR in Losada's study also showed no significant difference of DFS existed in either all breast cancer patients (P=0.45) or triple-negative breast cancer (TNBC) patients (P=0.09) (17). The reason may come from the following respects: one is the amount of studies correlated to the role of NMR in malignant cancer is too small; another may be explained by discrepancies in study population, treatment modality and pathological type.

Integrating LMR and NLR, we analyzed the prognostic relationship among LMR, NLR and ESCC, in which we found the patients in LMR ≥3.83 and NLR <2.06 group received the best prognosis when compared with that of other three groups and the prognosis of patients in LMR<3.83 and NLR ≥2.06 group was the worst. The difference was statistically significant. To our knowledge, seldom have the studies integrated the effect of LMR and NLR on ESCC patients, and what we have received from the study demonstrated that if the lymphocytes or/and monocytes count take the dominant place in tumor-related systemic inflammation, the ESCC patients will harvest the good prognosis, otherwise, the neutrophils will have adverse effect on patients' survival. Certainly, the further studies are also warranted to confirm the results.

Also, there're also some limitations in our study. First, our study is a single-center design, retrospective study and the analytical and selection biases were inevitable. In addition, it is difficult to compare our results with those of other studies, which used different cut-off points. As far as we know, we firstly applied R® to determine the optimal cut-off point for LMR, NLR and NMR, which can provide a value of a cut-off point that correspond to the most significant relation with survival. Therefore, it is unclear which is the best approach for cut-off determination and whether a different cutoff value would serve as a better predictor of tumor recurrence in ESCC. Thirdly, the prognostic significance of LMR, NLR and NMR were mainly focused on ESCC patients owing to the most patients with esophageal cancer in China are squamous cell carcinoma, however, the most esophageal cancer in western countries is adenocarcinoma. Thus, a multicenter collaborative prospective study is required to be further verified in a prospective, large-scale collaborative study.

In conclusion, different from the previous studies, we made used of R® to determine the optimal cut-off values and the preoperative LMR as well as NLR may be recognized as the convenient and inexpensive standard laboratory measurements for predicting the prognosis of ESCC patients who received the curative surgery. Meanwhile, better prognosis is associated with the dominant place of lymphocytes or/and monocytes in tumor-related systemic inflammation, however, neutrophils will counteract on prognosis. This finding may help clinicians to assess the prognosis of ESCC patients after operation. Still the further confirmation is warranted.

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Footnote

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