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The Prognostic Value of Biomarkers in Peripheral Blood for Esophageal Squamous Cell Carcinoma and the Construction of a Predictive Model

Xu Y[1#], Sun H[2#], Chen H[1], Zhao Y[1] and Wan C[1]**

[1]Molecular Laboratory, Changshu Medicine Examination Institute, China

[2]Central Laboratory, Nanjing First Hospital, Nanjing Medical University, China

[#]These authors contributed equally to this work

Abstract

As particular nonspecific biomarkers of systemic inflammation in the peripheral blood, the Neutrophil to Lymphocyte Ratio (NLR), derived NLR (dNLR) and Platelet to Lymphocyte Ratio (PLR) act as useful prognostic indicators in various cancers including Esophageal Squamous Cell Carcinoma (ESCC). Simultaneously, ABO blood group is assumed to be a potential marker for the prognosis of ESCC patients. Therefore, this retrospective analysis enrolled 495 ESCC patients to investigate the value of biomarkers for predicting the survival rate. The optimal cut-off values were determined by the Receiver Operating Characteristics curve (ROC curve). The association between biomarkers and clinicopathologic parameters were calculated by Pearson correlation analyses. The Kaplan-Meier method and Cox regression analyses evaluated the Overall Survival (OS) and prognostic factors, respectively. A predictive nomogram was established to predict survival risk. According to the ROC curve, the optimal cut-off values of NLR, dNLR and PLR were 2.67, 1.91 and 144. Moreover, patients with lymph node N1-N3, distant metastasis M1 showed higher level of NLR, dNLR and PLR compared with N0 and M0, and cases with stage III-IV had higher level of NLR and PLR compared with I-II (P_{all}<0.05). Multivariate Cox regression analysis indicated that tumor grade, stage, depth of invasion, distant metastasis and dNLR were independent prognosis risk factors. Furthermore, the nomogram could more accurately predict OS (c-index: 0.776) in surgical ESCC patients. In conclusion, dNLR is a prospective clinical efficacy predictor in ESCC patients. Moreover, the proposed nomograms can be used for the prediction of OS in ESCC patients undergoing esophagectomy.

Keywords: Esophageal squamous cell carcinoma; ABO blood group; NLR; dNLR; PLR; Prognosis

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Correspondence:

Chuandan Wan, Molecular Laboratory, Changshu Medicine Examination Institute, 36 Qingduntang Road, Suzhou, Jiangsu, China, Tel: +86 051252345208

Yilin Zhao, Molecular Laboratory, Changshu Medicine Examination Institute, 36 Qingduntang Road, Suzhou, Jiangsu, China

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Introduction

Human Esophageal Cancer (EC) is regarded as one of the most aggressive malignancies and was the ninth leading cancer and sixth leading cause of cancer-related mortality worldwide [1]. In China, ESCC is the main pathological type. Although advances have occurred in the multidisciplinary treatment in ESCC, its 5-year survival rates still remain poor, and it remains inadequately explored [2]. Therefore, it is of utmost significance to assess the prognostic factors in ESCC patients.

Generally agreed prognostic factors for ESCC including depth of invasion, lymph node metastasis, TNM stage and other miscellaneous factors have a close relationship with tumor burden [3]. Recently, emerging evidence have demonstrated that a systemic inflammatory response is of prognostic value in a variety of cancers [4,5]. The inflammatory response may result in an increased propensity for metastasis *via* upregulation of cytokines and inflammatory mediators, inhibition of apoptosis, promotion of angiogenesis and damage of DNA [6-8]. The NLR, dNLR and PLR in the peripheral blood are particular nonspecific markers of systemic inflammation and act as useful prognostic indicators in various kinds of cancers including ESCC [9-14]. Meanwhile, ABO blood group also has been discovered to be closely associated with the prognosis of various cancers [15-18]. However, as no consensus has been reached about the clinical and prognostic significance of these inflammatory biomarkers and ABO blood group in ESCC patients. Meanwhile, the previous literatures focused on only one or two of these biomarkers on prognosis for ESCC patients, and the optimal cut-off values of the biomarkers were still inconsistent.

Given the important role of inflammation in ESCC, we conducted this retrospective study to investigate preoperative NLR, dNLR and PLR as clinically prognostic predictors after attempted curative esophagectomy. Likewise, a well-designed investigation regarding a correlation between ABO blood group and prognostic significance of ESCC was performed as well. We also tried to establish a prognostic nomogram with improved predictive capacity for ESCC patients based on the biomarkers and the clinicopathologic features.

Materials and Methods

Patients

This retrospective analysis enrolled a total of 495 EC patients who were newly diagnosed in Nanjing First Hospital, Jiangsu, China between October 2005 and September 2012. All patients should match the criteria:

(1) pathologically confirmed as ESCC and classified by the 8th edition of the TNM-UICC/AJCC classification [19];

(2) no prior chemotherapy or radiotherapy pre-operation;

(3) estimated life expectancy ≥ 3 months post-operation;

(4) complete pathological, clinical and follow-up information were obtained from eligible patients.

(5) no inflammatory or autoimmune diseases or hematologic disorders.

Data collection

All peripheral blood was collected in tubes with Ethylenediaminetetraacetic Acid (EDTA) at pre-operation. Blood samples were detected by Sysmex XT-1800i Automated Hematology System (Shanghai, China) to measure white cell count, neutrophil count, lymphocyte count, platelet count pre-operation. Meanwhile, ABO blood type test was detected on the first admission.

The following data were also extracted: Age, gender, smoking history (ever or never), drinking history (ever or never), tumor grade and stage, depth of invasion, lymph node, distant metastasis and receipt of neoadjuvant therapy.

Definitions of the indexes

The definitions of NLR, dNLR and PLR were described as follows: NLR= absolute neutrophil count to absolute lymphocyte count; dNLR= absolute neutrophil count to (white blood cell count-absolute neutrophil count); PLR= absolute platelet count to absolute lymphocyte count.

Patient follow-up

All patients were followed up in outpatient clinics at regular intervals until July 2014 or until death at post-operation. First follow up was undertaken at 6 weeks following surgery and subsequently after 3, 6, 9 months, 1 year and thereafter at every six months interval. All subjects gave written informed consent to the study protocol, which was approved by the medical ethics committee of the Nanjing First Hospital, Nanjing Medical University. The mean follow-up time was 28.5 months ranging from 3 to 89 months. The OS was defined as the time from surgery to death. When patients did not die or lost to follow-up, the date of last follow-up was applied.

Statistical analysis

Statistical analysis was conducted by SPSS 22.0 software (SPSS Inc., Chicago, IL, USA), R 4.0.2 software (Institute for Statistics and Mathematics, Vienna, Austria) and GraphPad Prism 8 software. The ROC curve was plotted and calculated the optimal cut-off levels of NLR, dNLR and PLR. Chi-square test was used to analyze the relationship between clinicopathologic parameters and these biomarkers. The survival rates were compared by Kaplan-Meier method and Log-rank test. Furthermore, univariate and multivariate analyses were applied using Cox regression models to evaluate the effects of multiple covariates on survival outcomes. In addition, nomograms were established by R software and the predictive accuracy was evaluated by c-index, which ranged from 0 to 1. All P values less than 0.05 were considered statistically significant.

Results

Clinicopathologic characteristics of patients

Among the 495 ESCC patients, 391 (79.0%) were male and 104 (21.0%) were female, and the median age was 63.7 ± 9.4 years, with an age range from 43 to 88 years. All patients were treated with radical resection. Three hundred and 195 of the patients were confirmed as TNM I-II and III-IV stage, and the number of cases with tumor grade G1-G2 and G3-G4 was 84.0% and 16.0%, respectively. Moreover, there were 269 and 251 patients received adjuvant therapy including radiotherapy and chemotherapy, respectively. The clinicopathologic characteristics of these patients were shown in Table 1.

The optimal thresholds for NLR, dNLR and PLR

The Areas Under Curve (AUC) for NLR, dNLR and PLR were

Table 1: Clinical characteristics of 495 patients with ESCC.

Characteristics	Categories	No. of ESCC patients (%)
Gender	Male	391 (79.0%)
	Female	104 (21.0%)
Age (years)	<60	163 (32.9%)
	≥ 60	332 (67.1%)
Smoking	Yes	178 (36.0%)
	No	317 (64.0%)
Drinking	Yes	118 (23.8%)
	No	377 (76.2%)
Tumor grade	G1-G2	416 (84.0%)
	G3	79 (16.0%)
Tumor stage	I-II	300 (60.6%)
	III-IV	195 (39.4%)
Depth of invasion	T1-T2	184 (37.2%)
	T3-T4	311 (62.8%)
Lymph node	N0	286 (57.8%)
	N1-N3	209 (42.2%)
Distant metastasis	M0	434 (87.7%)
	M1	61 (12.3%)
Chemotherapy	Yes	269 (54.3%)
	No	226 (45.7%)
Radiotherapy	Yes	251 (50.7%)
	No	244 (49.3%)
ABO blood group	A	150 (30.3%)
	B	130 (26.3%)
	O	171 (34.5%)
	AB	44 (8.9%)

Table 2: ROC curve analysis of significant quantitative biomarkers.

Index	AUC	95% CI	*P* value	Cut-off value
NLR	0.577	0.525-0.626	0.004	2.67
dNLR	0.565	0.513-0.615	0.014	1.91
PLR	0.581	0.531-0.631	0.002	144

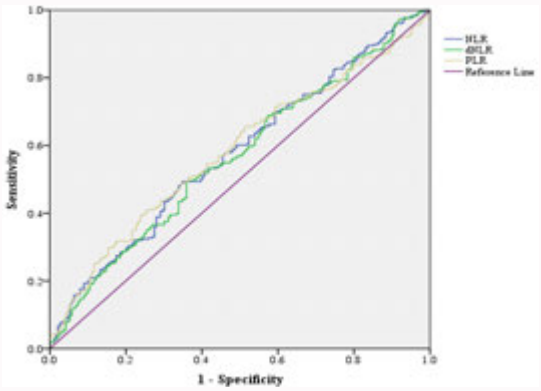

Figure 1: ROC analysis diagram of meaningful quantitative indicators.

0.577 (0.525-0.626), 0.565 (0.513-0.615) and 0.581 (0.531-0.631), respectively, which were described by ROC curves analysis (Table 2 and Figure 1). The optimal cut-off levels were 2.67 for NLR, 1.91 for dNLR and 144 for PLR (Table 2). Subsequently, according to these optimal cut-off levels, patients were divided into high groups that ≥ these optimal cut-off levels and low groups that <these optimal cut-off levels, respectively.

Correlations between NLR, dNLR, PLR, ABO group and clinicopathologic parameters

Clinicopathologic parameters were compared between the high and low groups for NLR, dNLR, PLR and between AB and non-AB blood type (Table 3). The NLR was significantly correlated with gender (P=0.026), age (P=0.012), tumor stage (P<0.001), depth of invasion (P=0.004), lymph node (P=0.013) and distant metastasis (P<0.001). Similarly, there were significant correlations between dNLR and tumor stage (P<0.001), depth of invasion (P=0.001), lymph node (P=0.012) and distant metastasis (P<0.001). Moreover, the PLR was significantly correlated with gender (P=0.043), tumor stage (P=0.004) and distant metastasis (P<0.001), and ABO blood type was associated with drinking (P=0.042), tumor stage (P=0.018), lymph node (P=0.035) and radiotherapy (P=0.035), shown in Table 3. Furthermore, the ESCC cases with lymph node N1-N3, distant metastasis M1 showed higher level of NLR, dNLR and PLR compared with N0 and M0, and cases with stage III-IV had higher level of NLR and PLR compared with stage I-II (P_{all}<0.05, (Table 4 and Figure 2)).

Correlations between baseline characteristics and clinical prognosis

Kaplan-Meier survival analysis and log-rank tests were conducted to evaluate the association between baseline characteristics and clinical prognosis based on the postoperative survival time and the pathological data of patients. Our results revealed that patients with NLR (<2.67), dNLR (<1.91) and PLR (<144) were significantly associated with better OS, respectively (P_{all}<0.05, Figure 3). Likewise, better OS was observed in cases with tumor grade (G1-G2), stage (I-II), depth of invasion (T1-T2), lymph node (N0), distant metastasis (M0) (P_{all}<0.05, (Figure 4)). However, no significant association between ABO blood group and OS was observed (P=0.087, (Figure 3)).

Prognostic factors affecting OS in the whole cohort

Univariate analysis demonstrated that tumor grade, stage, depth of invasion, lymph node, distant metastasis and inflammatory biomarkers (NLR, dNLR and PLR) were associated with OS of 495 ESCC patients (P_{all}<0.05, (Table 5)). Multivariate analysis indicated

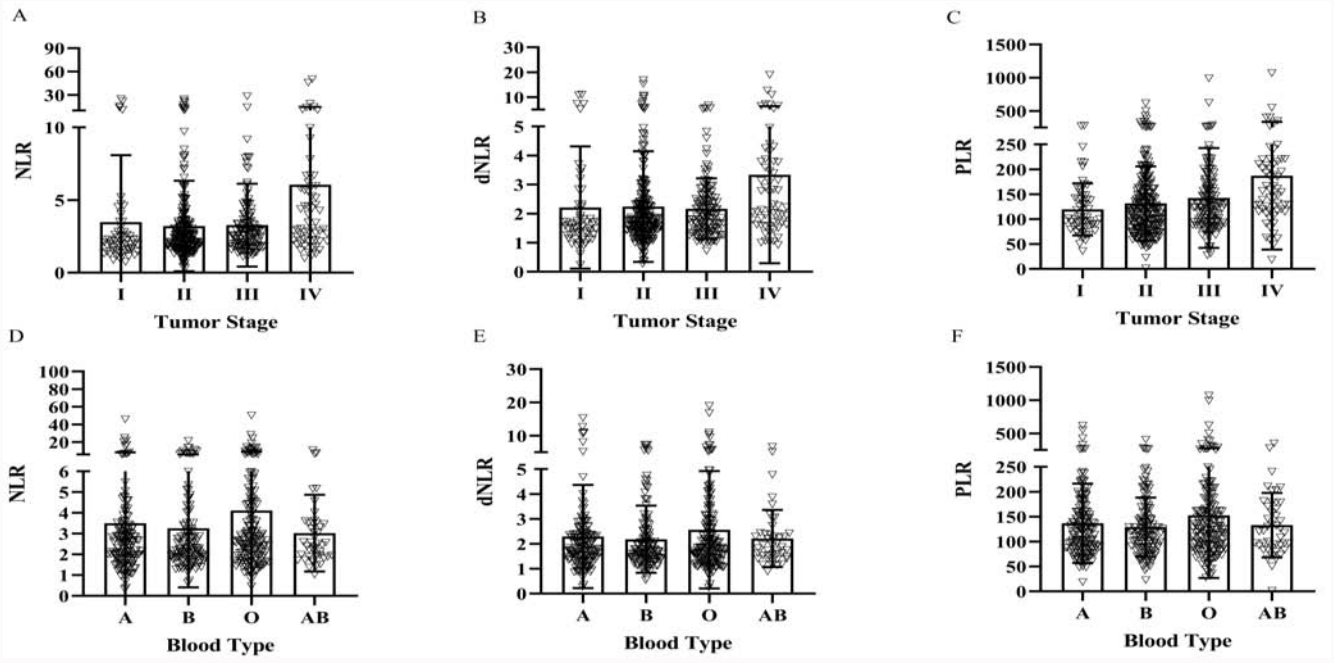

Figure 2: The relationship between NLR, dNLR, PLR and tumor stage, ABO blood group in patients with ESCC. A) the distribution of NLR level in different tumor stages. B) the distribution of dNLR level in different tumor stages. C) the distribution of PLR level in different tumor stages. D) the distribution of NLR level in different ABO blood groups. E) the distribution of dNLR level in different ABO blood groups. F) the distribution of PLR level in different ABO blood groups.

Table 3: Baseline patient characteristics according to total patients, NLR, dNLR, PLR level and ABO blood group.

Characteristics	Categories	Total patients	Patients grouped by NLR level (n=495)		p	Patients grouped by dNLR level (n=495)		p	Patients grouped by PLR level (n=495)		p	ABO blood type (n=495)					p
		(n=495)	NLR<2.67 (n=276)	NLR ≥ 2.67 (n=219)		dNLR<1.91 (n=274)	dNLR≥ 1.91 (n=221)		PLR<144 (n=325)	PLR ≥ 144 (n=170)		O (n=171)	A (n=150)	B (n=130)	AB (44)	Non-AB (451)	
Gender	Male	391	208	183	**0.026**	208	183	0.061	248	143	**0.043**	143	119	93	36	355	0.629
	Female	104	68	36		66	38		77	27		28	31	37	8	96	
Age (years)	< 60	163	104	59	**0.012**	99	64	0.091	103	60	0.418	55	54	42	12	151	0.403
	≥ 60	332	172	160		175	157		222	110		116	96	88	32	300	
Smoking	Yes	178	94	84	0.322	95	83	0.506	113	65	0.445	59	59	49	11	167	0.112
	No	317	182	135		179	138		212	105		112	91	81	33	284	
Drinking	Yes	118	68	50	0.639	67	51	0.721	75	43	0.582	36	47	30	5	113	**0.042**
	No	377	208	169		207	170		250	127		135	103	100	39	338	
Tumor grade	G1-G2	416	234	182	0.613	229	187	0.754	277	139	0.317	143	127	108	38	378	0.659
	G3	79	42	37		45	34		48	31		28	23	22	6	73	
Tumor stage	I-II	300	188	112	**<0.001**	188	112	**<0.001**	212	88	**0.004**	98	94	74	34	266	**0.018**
	III-IV	195	88	107		86	109		113	82		73	56	56	10	185	
Depth of invasion	T1-T2	184	118	66	**0.004**	119	65	**0.001**	130	54	0.072	61	55	47	21	163	0.129
	T3-T4	311	158	153		155	156		195	116		110	95	83	23	288	
Lymph node	N0	286	173	113	**0.013**	172	114	**0.012**	194	92	0.233	101	84	69	32	254	**0.035**
	N1-N3	209	103	106		102	107		131	78		70	66	61	12	197	
Distant metastasis	M0	434	256	178	**<0.001**	254	180	**<0.001**	298	136	**<0.001**	144	136	113	41	393	0.244
	M1	61	20	41		20	41		27	34		27	14	17	3	58	
Chemotherapy	Yes	269	149	120	0.858	148	121	0.87	176	93	0.907	95	84	63	27	242	0.327
	No	226	127	99		126	100		149	77		76	66	67	17	209	
Radiotherapy	Yes	251	149	102	0.101	147	104	0.145	174	77	0.081	90	72	60	29	222	**0.035**
	No	244	127	117		127	117		151	93		81	78	70	15	229	

Table 4: The relationship between ESCC patients' pathological data and inflammatory biomarkers level.

Characteristics	Categories	NLR	*P* value	dNLR	*P* value	PLR	*P* value
Tumor stage	I-II	3.26 ± 3.45	**0.032**	2.24 ± 1.94	0.106	129.18 ± 70.54	**0.004**
	III-IV	4.13 ± 5.48		2.53 ± 1.97		156.25 ± 118.62	
Tumor grade	G1-G2	3.60 ± 4.56	0.957	2.35 ± 2.00	0.938	138.97 ± 95.87	0.635
	G3	3.63 ± 3.31		2.34 ± 1.72		144.41 ± 79.06	
Depth of invasion	T1-T2	3.60 ± 4.20	0.998	2.42 ± 2.36	0.604	131.63 ± 76.93	0.132
	T3-T4	3.60 ± 4.48		2.31 ± 1.67		144.70 ± 101.62	
Lymph node	N0	3.20 ± 3.00	**0.029**	2.17 ± 1.47	**0.022**	131.24 ± 65.46	**0.028**
	N1-N3	4.15 ± 5.71		2.60 ± 2.45		151.62 ± 120.75	
Distant metastasis	M0	3.22 ± 3.15	**0.009**	2.19 ± 1.59	**0.003**	132.20 ± 77.76	**0.003**
	M1	6.32 ± 8.81		3.53 ± 3.39		194.23 ± 157.08	
Blood type	AB	3.02 ± 1.85	0.353	2.21 ± 1.14	0.627	132.90 ± 64.62	0.606
	non-AB	3.66 ± 4.55		2.36 ± 2.02		140.52 ± 95.71	

that tumor grade (P<0.001), tumor stage (P<0.001), depth of invasion (P=0.012), distant metastasis (P<0.001) and dNLR (P=0.010) were independent prognostic factors (Table 5).

Prognostic nomograms for OS in the whole cohort

To predict the survival risk of ESCC patients, a nomogram was established by multivariate Cox regression model according to all significantly independent factors and ABO blood groups for OS (Figure 5). The nomogram can predict the probability of death for ESCC patients within 3 or 5 years after initial surgery (c-index was 0.776).

Discussion

In the present study, the results revealed that the composite of pre-operation NLR, dNLR, PLR and clinical parameters (tumor grade, stage, depth of invasion, lymph node and distant metastasis) were significant predictors of prognosis in ESCC patients in the univariate analysis. However, in the multivariate analysis, only the

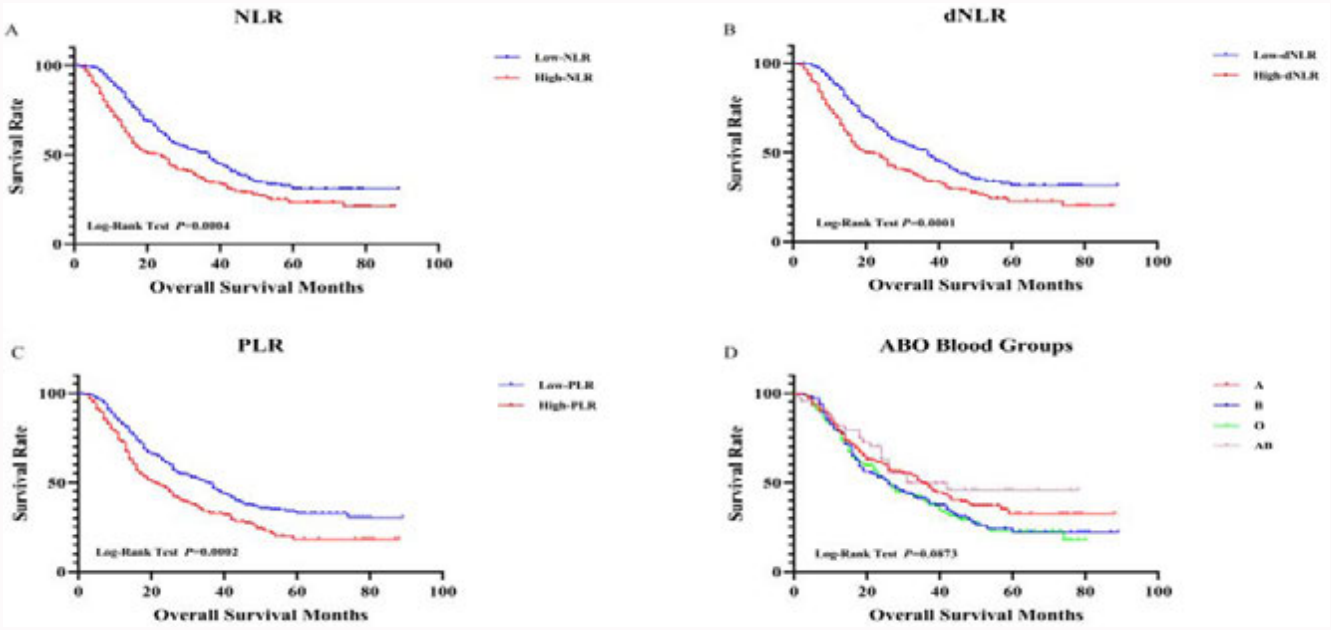

Figure 3: Kaplan-Meier curves for OS in ESCC patients according to tumor grade, tumor stage, depth of invasion, lymph node and distant metastasis. (A) Patients with grade G3 had a significant association with worse OS than those with grade G1-G2 (P<0.05). (B) Patients with stage III-IV had a significant association with worse OS than those with stage I-II (P<0.05). (C) Patients with T3-T4 had a significant association with worse OS than those with T1-T2 (P<0.05). (D) Patients with N1-N3 had a significant association with worse OS than those with grade N0 (P<0.05). (E) Patients with grade M1 had a significant association with worse OS than those with grade M0 (P<0.05).

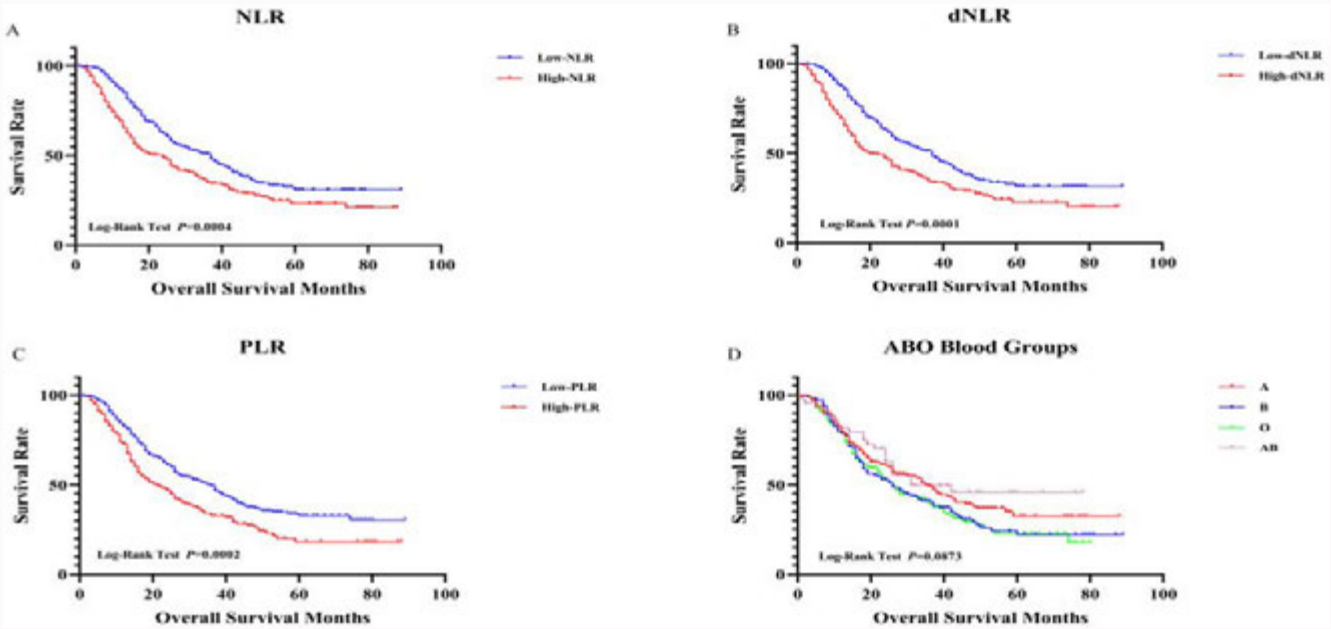

Figure 4: Kaplan-Meier curves for OS in ESCC patients according to NLR, dNLR, PLR level and ABO blood group. (A) Patients with NLR ≥ 2.67 had a significant association with worse OS than those with NLR<2.36 (P<0.05). (B) Patients with dNLR ≥ 1.91 had a significant association with worse OS than those with dNLR<1.91 (P<0.05). (C) Patients with PLR ≥ 144 had a significant association with worse OS than those with PLR<144 (P<0.05). (D) Patients with four ABO blood groups had no significant association with OS (P=0.087).

dNLR was an independent prognostic biomarker for OS, whereas other well-known biomarkers were not. Subsequently, a prognostic nomogram was established to improve the predictive accuracy. Taken together, dNLR is expected to be a useful inflammatory biomarker for prognosis in ESCC cases.

Accumulating evidence have proposed that inflammation is a hallmark of cancer initiation and promotion [20]. Emerging studies have shed a light that prognosis of cancer is determined not solely by tumor-related factors, but also by host response to systemic inflammation [21]. As a key component of peripheral blood, neutrophils play a critical role in host systemic immune response, but also involve in modulating the tumor microenvironment [22]. It is reported that cancer associated inflammatory factors like IF-6, TNF-α, IL-6, IL-8, IL-12 and myeloid growth factors could recruit

Table 5: The association of clinicopathological characteristics with OS in ESCC patients.

Characteristics	Univariate analysis		Multivariate analysis	
	HR	*P* value	HR (95% CI)	*P* value
Sex (Female)	1.001	0.996		
Age (≥ 60 years)	1.108	0.403		
Smoking (yes)	0.922	0.495		
Drinking (yes)	1.095	0.489		
Chemotherapy (yes)	0.995	0.962		
Radiation therapy (yes)	1.218	0.087		
O/AB	1.541	0.064		
A/AB	1.189	0.468		
B/AB	1.514	0.083		
Tumor grade (G3)	3.165	**<0.001**	2.594 (1.960-3.435)	**<0.001**
Tumor stage (III-IV)	4.242	**<0.001**	2.430 (1.784-3.310)	**<0.001**
Depth of invasion (T3-T4)	2.637	**<0.001**	1.484 (1.089-2.021)	**0.012**
Lymph node (N1-N3)	2.969	**<0.001**	1.285 (0.853-1.937)	0.23
Distant metastasis (M1)	7.643	**<0.001**	3.603 (2.578-5.037)	**<0.001**
NLR (≥ 2.67)	1.492	**<0.001**	1.240 (0.984-1.562)	0.068
dNLR (≥ 1.91)	1.547	**<0.001**	1.354 (1.075-1.706)	**0.01**
PLR (≥ 144)	1.522	**<0.001**	1.262 (0.999-1.594)	0.051

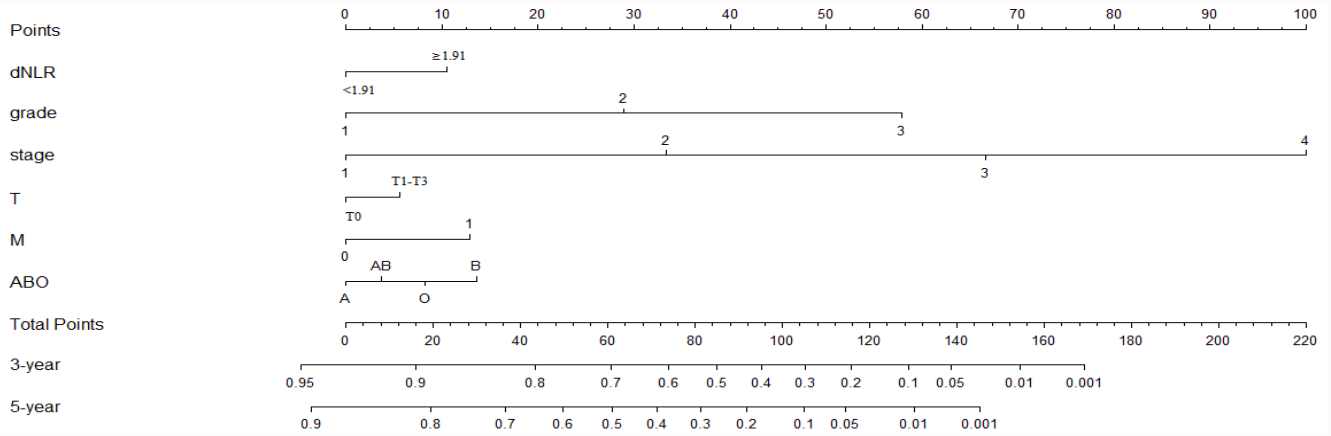

Figure 5: Postoperative nomogram with dNLR and significant clinicopathologic characteristics predicted the OS. The nomogram is used by adding the points identified at the top of the scale for each independent factor. Then, this total point score is identified on the total points scale to determine the probability of risk prediction.

neutrophils, which could promote secretion of Vascular Endothelial Growth Factor (VEGF) and Reactive Oxygen Species (ROS) [23-25]. ROS might induce cell DNA damage and genetic instability playing an important role in tumor microenvironment [26]. On the other hand, tumor cells could secret Granulocyte Colony Stimulating Factor (G-CSF), which trigger the neutrophils [27]. For inflammatory biomarker dNLR, which does not require lymphocytes count and closely connects with neutrophils count, is an easily available and inexpensive marker in clinical studies. Since Proctor et al. [28] conducted a retrospective cohort study of more than 12,000 cancer patients, they originally validated dNLR as an alternative to NLR in various cancers including esophageal cancer. However, the association between dNLR and ESCC is rare [10,29]. The current study revealed that dNLR was an independent prognostic biomarker for ESCC, which was in accordance with the previous literature [29]. However, the cut-off value was different, which was perhaps due to the differences in measure methods or genetic and environmental backgrounds among populations.

To the best of our knowledge, there is little evidence between ABO blood group and prognosis in ESCC patients. Moreover, the results of the previous literatures were controversial. There was no association between ABO blood group and OS in ESCC patients in our study, which was consistent with previously published studies [16,30,31]. On the contrary, Yang et al. [32] indicated that blood group O had a worse OS than non-O groups. Shiratori et al. [33] reported that patients with non-B blood groups had significantly worse OS than those with the B blood group. Qiu et al. [34] reported patients with blood type AB had a significantly worse OS than patients with non-AB type. The conflicting results might be due to the heterogeneity of populations or limited sample sizes. Nevertheless, several hypotheses were used to explain the association between ABO blood group and OS in ESCC patients, for instance, individuals with non-O blood

types more achievable infection with *Helicobacter pylori* [35], blood group antigens regulating the inflammatory process [36]. However, the direct biologic mechanisms underlying the ABO blood group and prognosis of ESCC were not elucidated. As a result, whether ABO blood group can be used to predict ESCC survival or not still needs to be further confirmed.

It is also of interest to establish a prognostic nomogram combining with various inflammatory biomarkers and ABO blood group to predict postoperative prognosis for patients with ESCC. The nomogram performed well in prediction of OS with an accuracy of C-index 0.776, which could be used to be an accurately prognostic prediction for patients with ESCC.

Finally, several possible limitations should be acknowledged for this study. First, this study was a retrospective study, which might exist selection bias during retrospective data collection. Second, there was no consensus for the cut-off values of NLR, dNLR and PLR. Third, the number of enrolled cases was relatively small. Therefore, our results need to be further verified in a prospective, large-scale collaborative study.

Conclusion

According to the findings of the current study, dNLR is an independent prognostic factors in ESCC patients, which is convenient, economical, and reproducible. However, future prospective studies with larger populations are required to validate our results and to clarify the potential mechanisms underlying the prognostic value of the dNLR.

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