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Prognostic Role of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in the Survival of Patients with Esophageal Cancer

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ABSTRACT

Background: Different factors can affect the future of a person with cancer. The patient's systemic inflammatory response is an important factor. Several inflammatory markers have been evaluated for measuring the patient's response to cancer. We evaluated neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) as prognostic factors for survival in patients with pathologically proven esophageal cancer.

Methods: In this retrospective cohort study, patients with pathologically approved esophageal cancer, who underwent surgical treatment in the cancer institute of Iran, were included. Demographic, pathological, and laboratory data of patients were obtained from the archive of medical records.

Results: In this study, 135 patients with esophageal cancer with a mean age of 60 were studied. The median time of the follow-up period was 21 months. Mean NLR and PLR were 7.05 and 898, respectively. Patients' survival had a significant relationship with their age, gender, tumor differentiation, receiving chemotherapy, absolute neutrophil count, total bilirubin, direct bilirubin, and NLR.

Conclusion: According to the results, in a multivariable investigation, it was demonstrated that a high NLR has a direct effect on patients' poor survival.

Keywords: Esophageal Cancer, Survival, Neutrophils, Lymphocytes, Platelets, Surgery, Esophagectomy

INTRODUCTION:

Esophageal cancer is a progressive neoplasm with a poor prognosis (1). It stands in 7th place among the most prevalent cancers. In 2018, this cancer was responsible for one death in every 20 deaths due to cancer (2). Despite the improvement in medical sciences, the prevalence of esophageal squamous cell carcinoma (SCC) is increasing, especially in the elderly (3, 4).

Treatment options for this cancer contain surgery, radiotherapy, chemotherapy, or a combination of them (5). Esophagectomy with or without neoadjuvant therapy is the choice treatment for esophageal cancer (6). However, some elderly patients can not tolerate chemoradiotherapy (7).

The five-year survival of patients with esophageal cancer was reported to be 18% (8). This indicates that despite advances in the diagnosis and treatment of the disease, patients' prognosis remains low (9). Different factors, including weight loss, smoking, and comorbidities, can play an essential role in the final fate of a cancer patient (10). The host's systemic inflammatory response is also one of these factors (11). Several studies have shown that inflammation caused by a tumor can be related to systemic inflammation of the body (12-14). This can play an important role in the progression of the tumor, the survival of the patient, and the extent of the tumor's susceptibility to treatment, especially chemotherapy, by influencing activities such as apoptosis and angiogenesis (11). So far, various markers have been studied to assess the inflammation caused by tumors. However, measuring some of these markers is expensive and difficult. Obviously, the systemic inflammatory response caused by the tumor can affect blood parameters (15, 16). Recent studies declared that factors related to systemic inflammatory response, such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), are prognostic factors that correlate with the survival of patients with some solid tumors (17). In this study, we evaluated these ratios as prognostic factors of survival in patients with esophageal cancer.

METHODS:

In this retrospective cohort study, we obtained data of 232 esophageal cancer patients from the Cancer Institute of Iran. After excluding 31 (13%) patients due to lack of medical record, 13 (6%) patients who were not esophageal cancer based on their medical record, and 53 (23%) patients because of non-response and loss to follow-up, we studied 135 esophageal cancer patients. Patients with pathologically approved esophageal cancer who underwent surgery in the Cancer Institute of Imam Khomeini Hospital Complex, Tehran, Iran, were included in this study from March 2008 to March 2015. The exclusion criteria were: 1) multiple primary malignancies, 2) previous hematological diseases, and 3) stage 4 of esophageal cancer.

Demographic, clinicopathological, and laboratory data of the patients were obtained from their medical records. All the included laboratory tests were performed within 10 days before the surgery and at least 8 days after neoadjuvant therapy. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. To calculate the survival, patients were followed up by phone calls in March 2020.

Statistical Analysis

We performed statistical analysis using SPSS version 25. Quantitative data were described as mean ± standard deviation, and qualitative data were presented with frequency tables. We performed univariate and multivariate analyses of the Cox regression proportional hazard model to evaluate the effect of different factors

on survival. Kaplan-Meier method was used to describe the survival in the subgroups of categorical variables, and Log-rank was reported. P-values less than 0.05 were considered statistically significant.

Our study was approved by the ethics committee of Tehran University of Medical Sciences (code: IR.TUMS.MEDICINE.REC.1398.296).

RESULTS:

Characteristics of the Patients

In this retrospective study, the medical files of 232 patients were evaluated. Thirty-one files were excluded due to incomplete data. In addition, we could not include 13 patients because of having exclusion criteria. We called 188 patients to assess their survival. Unfortunately, we lost the follow-up of 53 patients in this step. The loss of follow-up was random and mainly due to the change in the patients' telephone contact or address and the lack of the patients' contact detail in the hospital records.

Finally, 135 esophageal cancer patients with a mean age of 60.2 ± 11.70 were included in this study. The age range was from 25 to 88 years. The study population consisted of 70 males (51.9%) and 65 females (48.1%). Totally, 89 (65.1%) patients received neoadjuvant therapy. Among these, 13 received chemotherapy, 16 underwent radiotherapy, and 60 (44.4%) received chemoradiotherapy.

Tumor characteristics

Tumor morphology in the majority of patients (70.4%) was squamous cell carcinoma (SCC), and most of the patients had moderately differentiated cancer (33.3%). **Table 1** shows the tumor characteristics of the patients.

Table 1. Descriptive statistics of tumor characteristics, including topography, morphology, and differentiation

Characteristics		Code	Number*	Frequency (Percentage)
Primary Site (Topography)	Esophagus, proximal (upper) third	C15.3	2	1.5
	Esophagus, middle third	C15.4	16	11.9
	Esophagus, distal (lower) third	C15.5	30	22.2
	Esophagus, NOS	C15.9	43	31.9
Morphology	SCC	M-8070/3	95	70.4
	Adenocarcinoma	M-8140/3	15	11.1
	Others	-	25	18.5
Differentiation (Grade)	Well	Grade I	12	8.9
	Moderate	Grade II	45	33.3
	Poor	Grade III	10	7.4
	Undifferentiated	Grade IV	0	0
	Unknown, cannot be assessed	-	13	9.6

*The numbers for different subgroups of study variables did not sum up to 100% due to missing values

Table 2. Descriptive statistics of the patients' laboratory data within 10 days before surgery

Lab test	Units	Mean	Standard Deviation
WBC	U/ml	6485	3380
Neutrophil	U/ml	4197	2589
Lymphocyte	U/ml	1347	838
Platelet	U/ml	223120	75760
Hb	g/dl	11.8	1.74
NLR	-	7.05	24.70
PLR	-	898	3.94
Creatinine	mg/dl	0.97	0.72
AST	u/L	27.00	12.17
ALT	u/L	22.37	14.97
ALP	u/L	240.75	97.06
Total Bilirubin	mg/dl	1.00	0.32
Direct Bilirubin	mg/dl	0.24	0.12
Albumin	mg/dl	3.86	0.52
Total Protein	g/dl	6.64	0.62

Lab data

Table 2 shows descriptive statistics of the patients' laboratory data. The mean absolute neutrophil and lymphocyte count was 4197±2589 and 1347±838, respectively. NLR and PLR were calculated. Mean NLR was 7.05 ± 24.70, and mean PLR was 898±3.94.

Survival

The last follow-up date was 22nd April 2020. The median follow-up period was 21 months. The overall survival of our patients was 31.9%. Based on univariate analysis of the COX regression, gender, age, tumor topography, neoadjuvant chemotherapy, total WBC count, absolute neutrophil count, total bilirubin, direct bilirubin, and neutrophil to lymphocyte ratio were predictive of survival (**Table 3**). Multivariate analyses were performed by adjusting for age, gender, topography, tumor differentiation, and chemotherapy status. This analysis revealed that NLR is an independent prognostic factor for survival (**Table 4**).

The Kaplan-Meier analysis showed that the overall survival ?? of female patients is more than male patients (**Figure 1**). However, the difference is not statistically significant (log-rank=0.1)

As **Figure 2** illustrates, patients with moderately differentiated cancer had better survival than patients with poorly differentiated cancer (log-rank:0.0001).

DISCUSSION:

This study showed that the overall survival in esoph-

Table 3. Hazard Ratio (HR) and 95% Confidence Interval (CI) of univariate Cox regression between different variables and overall survival

Variables	Number	HR (95% CI)		P-value
Gender				
Male	70	Reference		-
Female	65	1.32 (0.78-1.99)		0.1*
Age (year)	135	1.01-1.04		0.006*
Topography				
Esophagus, NOS	43	Reference		-
Upper	2	1.18(0.28-4.97)		0.8
Middle	16	0.72(0.36-1.43)		0.3
Lower	30	0.67(0.38-1.18)		0.1*
Morphology				
Other	25	-	-	-
SCC	95	1.13	0.65-1.96	0.6
Adenocarcinoma	15	1.02	0.47-2.22	0.9
Differentiation (Grade)				
NOS	13	-	-	-
I	12	0.50	0.16-1.54	0.23*
II	45	1.23	0.57-2.66	0.59
III	10	1.88	0.68-5.23	0.22*
Chemotherapy				
NO	26	-	-	-
Yes	73	1.53	0.88-2.65	*0.1
Radiotherapy				
NO	27	-	-	-
Yes	76	0.99	0.56-1.74	0.9
WBC		1.00	1.00-1.00	0.03*
Neutrophil (٪)		1.008	0.99-1.02	0.25
Lymphocyte (٪)		0.98	0.96-1.009	0.26
Hb		0.97	0.86-1.10	0.6
PLT		1.001	0.99-1.004	0.6
Cr		1.12	0.86-1.45	0.3
AST		0.99	0.98-1.01	0.8
ALT		0.99	0.98-1.01	0.6
ALP		1.001	0.99-1.003	0.27
BILL.T		1.64	0.93-2.87	0.08*
BILL.D		2.86	0.58-14.10	0.1*
ALB		0.83	0.55-1.26	0.3
Total Protein		0.87	0.63-1.20	0.4
Neutrophil (n)		1.00	1.00-1.00	0.01*
Lymphocyte (n)		1.00	1.00-1.00	0.99
NLR		1.04	0.99-1.09	0.06*
PLR		1.005	0.95-1.06	0.8

'*' The significant level was 0.2 in the univariate model to include them in the multivariate model.

Table 4. Hazard ratio (HR) and 95% confidence intervals (CI) for different study variables based on multivariant cox regression analysis

Variables	Number	HR (95% CI)		P-value
Gender				
Male	70	Reference	Reference	-
Female	65	1.53	0.77-3.05	0.2
Age (year)		1.01	0.98-1.03	0.2
Topography				
Esophagus, NOS	43	Reference	Reference	-
Upper	2	2.19	0.43-11.01	0.3
Middle	16	0.91	0.39-2.14	0.8
Lower	30	0.58	0.27-1.27	0.1
Differentiation (Grade)				
NOS	13	Reference	Reference	-
I	12	0.41	0.12-1.45	0.1
II	45	1.04	0.42-2.55	0.9
III	10	3.04	1.01-9.07	0.04*
BILL.T		2.14	0.24-18.98	0.4
BILL.D		0.003	0-12.001	0.1
NLR		1.07	1.004-1.14	0.03*

'*' The significant level was 0.05.

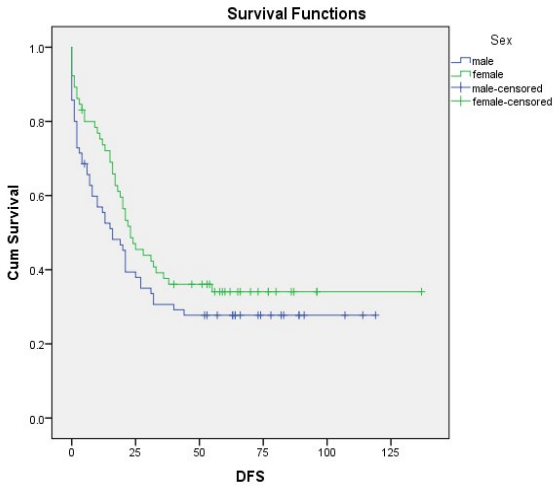

Figure 1. The most common prevalent cancers in Iran (both sexes)
Source: Global Cancer Observatory, https://gco. iarc.fr/today

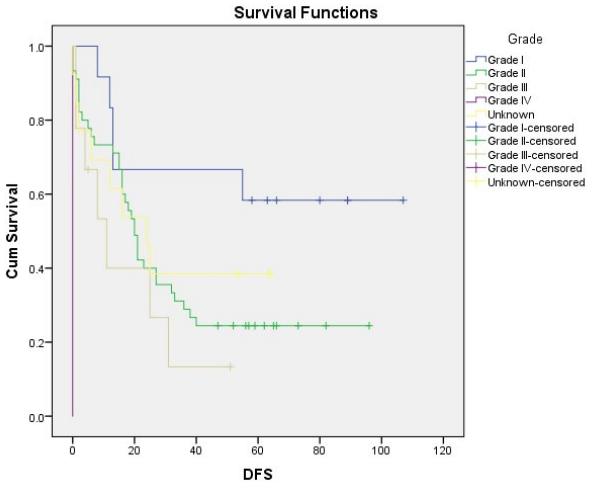

Figure 2. Comparison of overall survival in patients

ageal cancer patients is slightly associated with the neutrophil to lymphocyte ratio. However, we could not find any statistical relationship between platelet to lymphocyte ratio and overall survival.

Previous studies have introduced NLR as a prognostic inflammatory factor for overall survival in patients with colorectal, lung, and urinary system cancers. However, the prognostic role of this factor in esophageal cancer patients is still controversial.

In this study, multivariate analysis showed that higher NLR is associated with worse overall survival. In a systematic review in 2019, Pirozzolo et al. declared that NLR is an independent prognostic factor for overall survival (9). Sato et al. also showed that NLR is a relevant factor to body systemic inflammatory response, immune system status, and malnutrition among locally advanced and metastatic esophageal squamous cell carcinoma (18). They declared that high levels of this factor are a sign of immune deficiency. Some of the previous studies indicated that NLR did not have predictive power for esophageal cancer underwent surgical treatment (19, 20). These studies excluded patients with neoadjuvant therapy. There is no consensus on the reason for NLR's predictive role in cancer survival and chemotherapy response. Some researchers believe that inflammation caused by cancer results in increased inflammation cells, including neutrophils (21). Neutrophil proliferation decreases the antitumoral activity of Natural killer cells and activation of T-cells (22). In addition, neutrophils secrete factors including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and vascular endothelial growth factor (VEGF) that aggravate tumor growth (23). These factors may also cause leukocytosis (24).

Pre-inflammatory cytokines, including IL-1 and IL-6, are secreted due to cancer-related inflammation, resulting in megakaryocyte proliferation and thrombocytosis (21). The presence of neutrophilia and thrombocytosis is representative of nonspecific body response to the inflammation (25). Active platelets are essential sources for VEGF and transforming growth factor-β (TGF-β). VEGF and TGF-β improve angiogenesis and increase growth and invasion of the

tumor (26). A meta-analysis in 2016 showed that high levels of PLR could predict overall survival in patients with esophageal cancer who underwent surgical treatment (21). Although, this study indicated that PLR and NLR could not predict disease-free survival. Previous studies indicated that patients who received neoadjuvant chemoradiotherapy in addition to surgical treatment have better overall survival than those who only had surgical treatment (27). Chemotherapy could affect the neutrophil and lymphocyte count. Therefore, there should be a 6- to 8-week gap between neoadjuvant therapy and measuring NLR or PLR (9, 28). Our study had a gap of 6-7 weeks between neoadjuvant therapy and performing laboratory tests. Nobel et al. declared that absolute neutrophil count in patients with neoadjuvant therapy is significantly lower than others (29). McLaren and his colleagues showed that a high level of NLR and PLR predict poor response to neoadjuvant chemoradiotherapy (6). In our study, univariate Cox regression revealed a statistically significant relationship between neoadjuvant chemotherapy and overall survival.

Our study had some limitations, including missing data due to retrospective design. We suggest prospective studies with larger sample size and longer follow-up. In addition, we suggest that future studies evaluate patients for potential infections and inflammations or other conditions that can affect the neutrophil and lymphocyte counts.

CONCLUSION:

High levels of NLR indicate the activity of the innate immune system. This study showed that the level of NLR before surgery could be used as an independent prognostic factor for the overall survival of esophageal cancer patients. This test is easily accessible and has a reasonable price. In addition, this factor is a ratio and is not affected by different laboratory reports. Therefore, using NLR before surgery could help predict the results.

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