Prognostic significance of the neutrophil to lymphocyte ratio in patients with curative resection of esophageal cancer.
A single center experience

Ann Ital Chir, 2021 92, 3: 242-248
pii: S0003469X20032716
Online ahead of print 2021 - May 18
free reading: www.annitalchir.com

Fatih Dal*, Ugur Topal*/**, Erdogan Sozuer*/**, Tutkun Talih*, Doğan Gürkan İslam*, Hızır Yakup Akyıldız*/**

Erciyes University Medical Faculty, Melikgazi, Kayseri, Turkey
**Department of General Surgery*
***Department of Surgical Oncology*

Prognostic significance of the neutrophil to lymphocyte ratio in patients with curative resection of esophageal cancer. A single center experience

AIM: *In this study, we aimed to determine the clinical value and prognostic significance of the Neutrophil / Lymphocyte Ratio in patients undergoing curative surgery due to esophageal cancer.*
MATERIAL AND METHOD: *Patients who underwent curative resection for esophageal cancer between 2015-2019 were included in the study. Two groups, Group1 (low NLR) and Group2 (high NLR), were created. Demographic and clinical features, intraoperative and postoperative results, tumor characteristics and mean survival were compared in the groups.*
RESULTS: *A total of 48 patients participated in our study. Group 1 consisted of 18 patients and Group 2 consisted of 30 patients. Male sex was dominant in both groups (66.7% vs 73.3%, p. 0.431). Preoperative CEA was higher in Group 2 (3.97 vs 9.57, p. 0.032). Tumor diameter was larger in Group2 (3.33 vs 5.40 cm, p. 0.000). Adenocarcinoma was higher in Group 2 (33% vs 53.3%, p. 0.047), while squamous cell carcinoma was higher in Group 1 (66.7% vs 33.3%, p. 0.047). Lymph node positivity was higher in Group 2 (66.7% vs 93.3%, p. 0.024). The anastomosis leak was higher in Group 2 (0% vs 20%, p. 0.048). Postoperative hospital stay was longer in Group 2 (13.27 vs 23.9 days, p. 0.009). 90-day readmission was higher in Group1 (33.3% vs 3.3%, p. 0.008). Survival duration was shorter in Group 2 (29 vs 15 months, p. 0.005).*
CONCLUSION: *This study revealed that preoperative high NLR was associated with poor survival, along with greater tumor diameter, increased lymph node metastasis rate, and increased anastomosis leakage in patients with esophageal cancer. These results suggest that modifying inflammatory responses and modulating the immune system may improve survival outcomes in patients with esophageal cancer.*

KEY WORDS: Esophagus cancer, Neutrophil/lymphocyte ratio, Preoperative neutrophil/lymphocyte ratio, Prognosis

Introduction

Esophageal cancer is the seventh most common cancer worldwide, representing 3.2% of all cancers and constitute 5.3% of cancer-related deaths [1]. The primary curative treatment for esophageal cancer is esophagectomy with or without neoadjuvant therapy. Despite remarkable progress in the advancement of multidisciplinary therapies that combine surgery, chemotherapy and/or radiotherapy, the treatment results of patients with esophageal cancer remain negative even after full resection, esophageal cancer mortality rate is still high, and the 5-year survival rate has been reported to range from 15 to 25% [2-4].
The tumor-node-metastasis (TNM) stage is the most important prognostic factor. However, many studies have

Pervenuto in Redazione Febbraio 2020. Accetttao per la pubblicazione Marzo 2020
Correspondence to: Uğur Topal, MD, Department of General Surgery, Erciyes University Faculty of Medicine, 38030 Melilgazi/Kayseri, Turkey, (e-mail: sutopal2005@hotmail.com)

found that the prognosis is different even for patients at the same TNM stage. Therefore, defining other prognostic factors is important in determining appropriate treatment strategies [5,6].

In the literature, it has been found that systematic inflammatory response (SIR) plays an important role in tumor formation and progression [7]. It has been suggested that the neutrophil/lymphocyte ratio (NLR), considered a biomarker of SIR, reflects the balance between pro-tumor inflammation and anti-tumor immune function [8]. Based on this, inflammatory and immunological based scores that can be easily applied in daily oncological practice have been derived. NLR has been proved to be a consistent prognostic marker in various tumor types [9,10].

However, few studies have evaluated the prognostic utility of NLR in patients with esophageal cancer [11,12].

In this study, we aimed to determine the relationship of Neutrophil / Lymphocyte Ratio with postoperative complications and prognosis in patients undergoing curative surgery due to esophageal cancer.

Material and Method

48 patients who underwent curative esophagectomy for esophageal cancer between 2015 and 2019 participated in our study. A common database was created by examining patient files and hospital information system records. Patients were analyzed retrospectively using this database. Patients undergoing palliative surgery, those with Stage 4 disease, patients under the age of eighteen, pregnant patients, those with chronic inflammatory (Tuberculosis, Sarcoidosis) disease, autoimmune disease, patients with hematological disease, those using steroids, those with a pathological diagnosis other than a malignancy, and patients whose records could not be accessed were excluded from the study.

A cutoff value was determined with ROC curves. Two groups, Group 1 (low NLR) and Group 2 (high NLR), were created based on this cutoff value. Demographic and clinical features of the patients in these groups, body mass index (BMI), ASA score, localization (upper 1/3 and cervical esophagus, Middle 1/3, Lower 1/3, GOJ, and cardia) pathological type, degree of differentiation, TNM stage, total and metastatic lymph nodes dissected, lymph node positivity, tumor diameter, anastomosis type, operation duration, mean blood loss, intraoperative complications, additional organ resection, postoperative complication status according to the Clavien-Dindo classification 13, respiratory and cardiac complications, wound infection, anastomosis leakage, postoperative hospitalization, 90-day mortality, 90-day unplanned admission to the hospital and reoperation, whether long-term anastomosis stenosis developed, and mean survival were compared between the two groups.

Anastomosis leak was defined as a disruption in the integrity of the anastomosis documented by the combination of clinical, radiological and operative tools. Wound infection was defined as a superficial or deep incisional surgical area infection occurring in the surgical wound, according to the definition of the Centers for Disease Control (CDC) [14]. Tumor-node-metastasis (TNM) 2010 or 2016 system was used for tumor staging [15,16].

The total blood count was measured by an automated hematology analyzer (Roche Hitachi Cobas® 8000 Roche Diagnostics, Indianapolis, IN, USA)

Operation Technique

Transthoracic esophagectomy, open resection of the esophagus employing thoracotomy, including all single-, 2- and 3-stage procedures utilizing either a right or left thoracotomy or thoracoabdominal incision.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). Pearson Chi-square test statistics were used to compare categorical variables. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. In comparing continuous measurements between groups, distributions were checked, independent student t-test was used for parameters with normal distribution, and Mann Whitney U test was used for parameters without normal distribution. In the study, the neutrophil / lymphocyte ratios were based on the sensitivity and specificity values, the area under the ROC curve was calculated, and the cutoff value was determined. Kaplan-Meier analysis and Log Rank tests were used in survival analyzes. Statistical significance level was taken as 0.05 in all tests.

Results

A total of 48 patients participated in our study. Group 1 consisted of 18 patients and Group 2 consisted of 30 patients. The average age of the patients was similar (64 vs 60 years, p: 0.306) and male sex was dominant in both groups (66.7% vs 73.3%, p: 0.431). Patients were most commonly ASA 2 in both groups (61% vs 56.7%, p:0.829). The Body Mass Index (p: 0,709), preoperative Hgb (gr/dl) level (p: 0.644), preoperative albumin (gr/dl) level (p: 0.749) were similar between the groups. Preoperative CEA was higher in Group 2 (3.97 vs 9.57, p: 0.032). The most common tumor localiza-

TABLE I - *Demographic characteristics and preoperative findings of the patients*

		Group 1 Low NLR (n: 18)	Group 2 High NLR (n: 30)	p*
Age (min-max)		64.33±8.51 (52-80)	60.26±15.27 (27-86)	0.306
Sex	Male	12 (66.7)	22 (73.3)	0.431
	Female	6 (33.3)	8 (26.7)	
ASA score	1	4 (22.2)	9 (30.0)	0.829
	2	11 (61.1)	17 (56.7)	
	3	3 (16.7)	4 (13.3)	
BMI (min-max)		23.33±4.45 (16-30.2)	22.90±3.48 (18-33.9)	0.709
Preoperative Hgb (gr/dl) (min-max)		13.24±1.30 (11.3-14.7)	12.89±3.03 (7.3-18.6)	0.644
Preoperative albumin (gr/dl) (min-max)		3.92±0.66 (2.5-4.7)	3.97±0.45 (2.97-4.5)	0.749
Preoperative CEA (min-max)		3.97±4.33 (0.79-13.9)	9.57±10.19 (0.5-41.3)	0.032*
Tumor localization	Lower 1/3	10 (55.6)	22 (73.3)	0.226
	Lower 1/3+Cardia	4 (22.2)	3 (10.0)	
	Middle 1/3	2 (11.1)	4 (13.3)	
	Cervical esophageal	2 (11.1)	0 (0.0)	
	Total involvement	0 (0.0)	1 (3.3)	

TABLE II - *Intraoperative characteristics*

		Group 1 Low NLR (n: 18)	Group 2 High NLR (n: 30)	p*
Anastomosis technique	Hand-sewn	6 (33.3)	4 (13.3)	0.101
	Stapler	12 (66.7)	26 (86.7)	
Operation duration (min-max)		276.66±83.01(150-450)	271.83±97.65(140-540)	0.699
Intraoperative blood loss (min-max)		255.55±183.95(50-600)	211.66±142.73(10-600)	0.360
Intraoperative complication	No	16 (88.9)	30 (100.0)	0.136
	Yes	2 (11.1)	0 (0.0)	
Additional organ resection	Splenectomy	0 (0.0)	2 (6.7)	0.386
	None	18 (100.0)	28 (93.3)	

tion was the Lower 1/3 in both groups (55.6% vs 73.3%, p:0.226). Demographic and clinical characteristics are shown in Table I.

The anastomosis technique was similar in both groups, staplers were predominant (66.7% vs 86.7%, p: 0.101). Operation duration (276 min vs 271 min, p: 0.699), intraoperative blood loss (255 ml vs 211 ml, p: 0.360) were similar between the groups. In group 1, two patients had intraoperative complications. Splenectomy was performed in two patients in Group 2. Intraoperative features are shown in Table II.

Tumor diameter was larger in Group 2 (3.33 cm vs 5.40 cm, p: 0.000). Adenocarcinoma was higher in Group 2 (33% vs 53.3%, p: 0.047), while squamous cell carcinoma was higher in Group 1 (66.7% vs 33.3%, p: 0.047). The differentiation degrees were similar (p: 0.271). T3 (44.4% vs 53.3%, p: 0.271) and lymph node stage N1 (77.8% vs 93.3%, p: 0.1131) was most common in both groups. Stage 3B (33.3% vs 63.3%, p: 0.094) was the most common in both groups. The number of dissected (p: 0.797) and metastatic lymph nodes (p: 0.616) were similar. Lymph node positivity was high in Group 2 (66.7% vs 93.3%, p: 0.024). Pathological features are shown in Table IV.

Postoperative complications were pulmonary (p: 0.354) and cardiac complications (p: 0.141). The anastomosis leakage was higher in Group 2 (0% vs 20%, p: 0.048). Wound infection was more common in Group 2 (11.1% vs 20%, p: 0.357). Most commonly, there were Clavien-Dindo class 2 complications (66.7% vs 46.7%, p: 0.264). There was no 90-day reoperation. Postoperative hospital stay was longer in Group 2 (13.27 days vs 23.9 days, p: 0.009). In Group 1, 90-day readmission (33.3% vs 3.3%, p: 0.008) and anastomosis stenosis (22.2% vs 0%, p: 0.016) were higher. In terms of the current status, there are more patients with exitus in Group 2 (33.3% vs 66.7%, p: 0.026). It is shown in Table IV.

Survival time was shorter in Group 2 (29 months vs 15 months, p: 0.005). It is shown in Fig. 1 and Table V.

Discussion

Inflammation plays a critical role in the onset and development of the tumor [17]. Inflammatory cells and cytokines provide a favorable microenvironment, promoting tumor growth by facilitating the proliferation, angiogenesis and apoptosis inhibition of cancer cells. As one of

TABLE III - *Tumor characteristics*

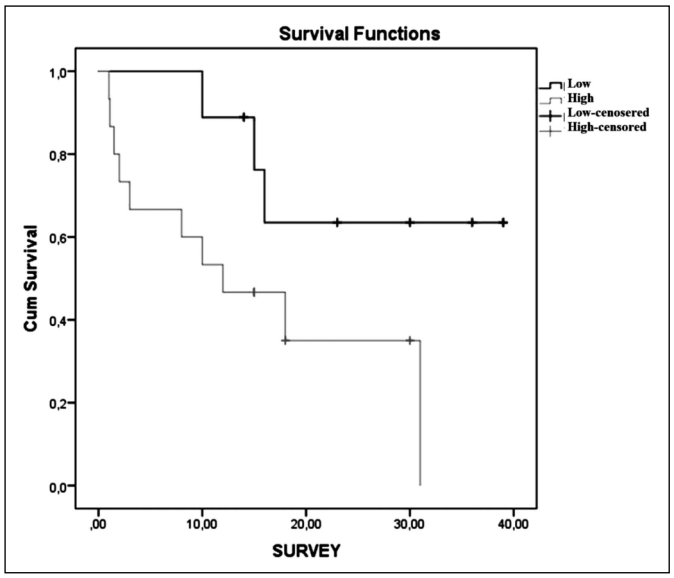
		Group 1 Low NLR (n: 18)	Group 2 High NLR (n: 30)	p*
Tumor diameter (min-max)		3.33±1.09(1.5-4.5)	5.40±1.43(3.5-9)	0.000*
Pathology	Adenocarcinoma	6(33.3)	16 (53.3)	0.047*
	Adeno-squamous	0 (0.0)	4 (13.3)	
	SCC	12 (66.7)	10 (33.3)	
Differentiation	High grade	6 (33.3)	14 (46.7)	0.271
	Low grade	4(22.2)	2 (6.7)	
	Middle grade	8 (44.5)	12 (40.0)	
	Signet ring	0 (0.0)	2 (6.7)	
Pathological T	T1	2(11.1)	2 (6.7)	0.271
	T2	6 (33.3)	4 (13.3)	
	T3	8 (44.4)	16 (53.3)	
	T4	2 (11.1)	8 (26.7)	
Pathological N	N0	4 (22.2)	2 (6.7)	0.131
	N1	14 (77.8)	28 (93.3)	
Pathological TNM	Stage 1B	4(22.2)	4 (13.3)	0.094
	Stage 2B	6 (33.3)	2 (6.7)	
	Stage 3A	2 (11.2)	5 (16.6)	
	Stage 3B	6 (33.3)	19 (63.3)	
Total number of dissected lymph nodes (min-max)		27.22±9.68(16-44)	26.33±11.05(10-52)	0.779
Number of metastatic lymph nodes		6.22±7.19(0-24)	7.2±6.04(0-18)	0.616
Lymph Node Positivity	Yes	12 (66.7)	28 (93.3)	0.024*
	No	6 (33.3)	2 (6.7)	

TABLE IV - *Perioperative and Postoperative Clinical Outcomes, Oncological outcomes*

		Group 1 Low NLR (n: 18)	Group 2 High NLR (n: 30)	p*
Respiratory complication	None	16 (88.9)	22 (73.3)	0.354
	Pneumonia	0 (0.0)	2 (6.7)	
	Unplanned reintubation	2 (11.1)	6 (20.0)	
Cardiac complication	Cardiac arrest	0 (0.0)	4 (13.3)	0.141
	None	18 (100.0)	26 (86.7)	
Anastomosis leakage	Yes	0 (0.0)	6 (20.0)	0.048*
	No	18 (100.0)	24 (80.0)	
Wound complication	Yes	2 (11.1)	6 (20)	0.353
	No	16 (88.9)	24 (80)	
Complication by Clavien-Dindo	Grade 2	12 (66.7)	14 (46.7)	0.264
	Grade 3a	4 (22.2)	10 (33.3)	
	Grade 3b	2 (11.1)	2 (6.7)	
	Grade 5	0 (0.0)	4 (13.3)	
90-day reoperation	No	18 (100.0)	30 (100.0)	1.000
	Yes	0 (0.0)	0 (0.0)	
Postoperative hospitalization (min-max)		13.27±5.35(7-26)	23.9±16.04(10-60)	0.009*
90-day readmission	No	12 (66.7)	29 (96.7)	0.008*
	Yes	6 (33.3)	1 (3.3)	
Anastomosis stenosis	No	14 (77.8)	30 (100.0)	0.016*
	Yes	4 (22.2)	0 (0.0)	
Current status	Ex	6 (33.3)	20 (66.7)	0.026*
	Alive	12 (66.7)	10 (33.3)	

the inflammatory parameters, NLR is a promising index to estimate the prognosis of cancer [10,18-20]. Potentially, the main cause of relapse after curative operation may be the growth of micrometastases occurring before resection, and a high neutrophil level correlates with the development of relapse, as the continuous systemic inflammatory response creates a favorable environment for micrometastatic growth. Lymphocytes, on the other hand, play an important role in anti-tumor immunity. The absolute lymphocyte count is assumed to reflect the degree of responsiveness of the entire immune system of a cancer patient, therefore, reduction in lymphocytes is thought to be associated with relapse [21,28].

H. Yodying et al. in their metanalysis about the pro-



Graph 1. Survival duration by groups.

TABLE V - *Survival duration by type of operation (alive)*

Groups	Average (Mean + sd (Min-Max))	p
Group 1	29.81±3.01 (23.9-35.71)	0.005*
Group 2	15.52±2.41 (10.79-20.25)	

gnostic value of NLR in esophageal cancer, found higher lymph node metastasis in the group with a high NLR rate, and this was a predictor for lymph node positivity (OR 2.14, 95% CI, 1.12-4.08, P= 0.009). High NLR was associated with deeper tumor invasion (OR 2.11, 95% CI, 1.23-3.60, P= 0.007). In the same study, NLR was not associated with tumor differentiation or vascular invasion [11]. Feng JF et al. found the rate of patients with tumor diameter greater than 3 cm to be higher in the group with high NLR in their series (44% vs 81%, p: 0.018) 23Similarly, Fu, X et al found significantly higher rate of tumor diameter larger than 5 cm in the group with higher NLR (p <0.001) [24]. In many studies in the literature, there was no relationship between the histological type of the tumor and NLR [25,26]. In our series, the tumor diameter was higher in the group with a high NLR (3.33 cm vs 5.40 cm, p: 0.000), supporting the literature. We found lymph node positivity to be higher in the group with high NLR (66.7% vs 93.3%, p: 0.024). Tumor marker level was also associated with NLR. Unlike the literature, adenocarcinoma was higher in the high NLR group (33% vs 53.3% p: 0.047), and squamous cell carcinoma was higher in the low NLR group (66.7% vs 33.3%, p:0.047).

The mechanism underlying the relationship between systemic inflammation and postoperative complications is that subclinical inflammation is exaggerated by the stress caused by the surgery. Excessive postoperative systemic inflammatory response syndrome causes a storm of cytokines that cause microcirculatory disorders in all organs. This causes wound healing impairment and increased infectious complications [27]. Respiratory complications, cardiac complications, and medical complications were not associated with NLR in our series. While wound problems of the surgical complications were not related, high NLR increased anastomosis leakage. Due to the management of anastomosis leaks, the length of hospital stay was prolonged in these patients. As expected, high NLR was associated with short-term postoperative complications, but was not associated with anastomosis stenosis and unplanned admissions to the hospital within 90 days.

The mechanisms by which NLR is associated with survival in esophageal cancer and other solid tumors are still uncertain. Tumors produce inflammatory cytokines and chemokines and are infiltrated by leukocytes, but advanced neoplasms are associated with a defective systemic immune response [28]. In the meta-analysis of H. Yodying et al on the prognostic value of NLR, patients with preoperative high NLR had significantly lower mean survival than those with a low NLR (OR 1.40, 95% CI, 1.08-1.81, P = 0.01) [8]. Similarly, in the metanalysis of Zhang, X et al., NLR significantly predicted poor OS (1.390, 95% CI: 1.235-1.545) of esophageal cancer patients [5]. Survival was significantly shortened in the group with high NLR in our series. In addition, in our last evaluation, the number of patients who died was higher in the group with higher NLR (33% vs 66.7%, p: 0.026).

The most important limitation of our study was that it was designed retrospectively. However, we believe it contributes to the literature, given the low incidence of esophageal cancer. Larger patient series are needed to determine appropriate cutoff values.

NLR is an easy-access and cheap biomarker. As a result, NLR can be used as a prognostic marker in patients with esophageal cancer undergoing curative resection. In addition, complications such as postoperative anastomosis leakage have developed more frequently in patients with high NLR.

Riassunto

Questo studio è finalizzato a determinare il valore clinico e il significato prognostico del rapporto neutrofili / linfociti (NLR) in pazienti sottoposti a chirurgia curativa per cancro dell'esofago.

Sono stati inclusi nello studio i pazienti sottoposti a resezione curativa per carcinoma esofageo tra il 2015-2019, suddividendoli in due gruppi, Gruppo 1, con NLR basso e Gruppo 2 con NLR alto. Nei gruppi sono state confrontate le caratteristiche demografiche e cliniche, i risultati intraoperatori e postoperatori, le caratteristiche del tumore e la sopravvivenza media.

Hanno partecipato al nostro studio un totale di 48 pazienti hanno. Il gruppo 1 era composto da 18 pazienti e il gruppo 2 era composto da 30 pazienti. Il sesso maschile era dominante in entrambi i gruppi (66,7% vs73,3%, p: 0,431). Il CEA preoperatorio era più elevato nel Gruppo 2 (3.97vs9.57, p: 0.032). Il diametro del tumore era maggiore nel Gruppo 2 (3,33 vs5,40 cm, p: 0.000). L'adenocarcinoma era di grado più elevato nel Gruppo 2 (33% contro 53,3%, p: 0,047), mentre il carcinoma a cellule squamose era più rappresentato nel Gruppo 1 (66,7% contro 33,3%, p: 0,047). La positività dei linfonodi era più elevata nel Gruppo 2 (66,7% vs 93,3%, p: 0,024). La deiscenza anastomotica è stata maggiore nel Gruppo 2 (0% vs 20%, p: 0,048). La degenza post-operatoria è stata più lunga nel Gruppo 2 (13,27 contro 23,9 giorni, p: 0,009). Un nuovo ricovero a 90 giorni si è verificato nel Gruppo 1 (33,3% vs 3,3%, p: 0,008). La durata della sopravvivenza è stata più breve nel Gruppo 2 (29vs15 mesi, p: 0,005).
Questo studio ha rivelato che un elevato NLR preoperatorio si è associato a una scarsa sopravvivenza, insieme a un maggiore diametro del tumore, a un aumento del tasso di metastasi dei linfonodi e ad una maggiore incidenza di deiscenza anastomotica in questi pazienti con carcinoma esofageo. Questi risultati suggeriscono che la modifica delle risposte infiammatorie e la modulazione del sistema immunitario possono migliorare gli esiti di sopravvivenza nei pazienti con carcinoma esofageo.

References

1. Bray F, Ferlay J, Soerjomataram I, et al.: *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA Cancer J Clin, 2018; 68:394-424.

2. Enzinger PC, Mayer RJ: *Esophageal cancer*. N Engl J Med, 2003; 349:2241-252.

3. Ishibashi Y, Tsujimoto Hiraki S, Kouz K, Tsuchiya S, Itazaki Y, et al.: *Predictive value of immuno-inflammatory and nutritional measures modulated by neoadjuvant chemotherapy on the response of neoadjuvant chemotherapy and long-term outcomes in patients with esophageal cancer*. Oncology Letters, 2020; 19:487-97.

4. Divisi D, Garramone M, Di Leonardo, Valente D, Torresini G, Di Giacop G, et al.: *Multimodal treatment for oesophageal primary cancer. A preliminary study*. Ann Ital Chir, 2009; 80:351-56.

5. Zhang X, Jiang Y, Wang Y, Wang Z, Zhao L, Xue X, et al.: *Prognostic role of neutrophil–lymphocyte ratio in esophageal cancer: A systematic review and meta-analysis*. Medicine, 2018; 97: e13585.

6. D'Amata G, Izzo L, Pugliese F, Izzo S, Izzo P, Costi U, et al: *New prognostic factors in gastric cancer: the role of lympho-plasmacytic infiltrate.* Ann Ital Chir, 2018; 89:398-405.

7. Mantovani A, Allavena P, Sica A, Balkwill F: *Cancer-related inflammation*. Nature, 2008; 454:436-44.

8. Maeda K, Shibutani M, Otani H, Nagahara H, Ikeya T, Iseki Y, et al.: *Inflammation based factors and prognosis in patients with colorectal cancer*. World J Gastrointest Oncol, 2015; 7:111-17.

9. Templeton J, McNamar, MG, Šeruga B, Vera-Badillo FE, Ane P, Ocaña, et al.: *Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis.* JNCI: Journal of the National Cancer Institute, 2014; 106:1-11.

10. Yalav, Topal U, Unal AG: *Clinical value of neutrophil/lymphocyte ratio in predicting postoperative complications, lymph node positivity and prognosis in gastric cancer patients who underwent curative surgical resection*. 2019; 26(11):2513-19.

11. Yodying H, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M, Uchida E: *Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis*. Annals of surgical oncology, 2016; 23:646-54.

12. Pirozzolo G, Gisbertz SS, Castor, C, van Berge Henegouwen MI, Scarpa M: *Neutrophil-to-lymphocyte ratio as prognostic marker in esophageal cancer: A systematic reviewand meta-analysis*. Journal of thoracic disease 2019; 11: 3136- 3145.

13. Clavien Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al: *The Clavien-Dindo classification of surgical complications: five-year experience*. Annals of surgery, 2009; 250:187-96.

14. American College of Surgeons: *User Guide for the 2012* ACS NSQIP Participant Use Data File

15. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, (eds): *AJCC cancer staging manual* (7th ed). New York, NY: Springer; 2010.

16. Hortobagyi GN, Connolly JL, Edge SB, et al.: *Breast.* In: Amin MB, Edge S, Greene G, et al. (eds): *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer International Publishing; 2016.

18. Shalapour S, Karin M: *Immunity, inflammation, and cancer: An eternal fight between good and evil*. J Clin Invest, 2015; 125: 3347-355.

19. Munn LL: *Cancer and inflammation*. Wiley Interdiscip Rev Syst Biol, 2017; 9:13.

20. Lin WW, Karin M: *A cytokine-mediated link between innate immunity, inflammation, and cancer.* J Clin Invest, 2007; 117:1175-183.

21. Shibutani M, Maeda K, Nagahara H, Ohtani H, Iseki Y, Ikeya T, et al.: *The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer.* World journal of surgical oncology, 2015; 13:194.

22. Cézé N, Thibault G, Goujon G, Viguier J, Watier H, Dorval E, et al.: *Pretreatment lymphopenia as a prognostic biomarker in colorectal cancer patients receiving chemotherapy*. Cancer Chemother Pharmacol, 2011; 68:1305-13.

23. Feng JF, Huang Y, Zhao Q, Chen QX: *Clinical significance of preoperative neutrophil lymphocyte ratio versus platelet lymphocyte ratio in patients with small cell carcinoma of the esophagus.* Scientific World Journal, 2013; 504365:1-7.

24. Fu X, Li T, Dai Y, Li J*: Preoperative systemic inflammation score (SIS) is superior to neutrophil to lymphocyte ratio (NLR) as a predicting indicator in patients with esophageal squamous cell carcinoma*. BMC cancer, 2019; 19:721.

25. Nakamura K, Yoshida N, Baba Y, Kosumi K, Uchihara T, Kiyozumi Y, et al.: *Elevated preoperative neutrophil-to-lymphocytes ratio predicts poor prognosis after esophagectomy in T1 esophageal cancer*. International journal of clinical oncology, 2017; 22: 469-75.

26. Grenader T, Waddel, Peckitt Oate J, Starlin N, Cunningha Bridgewater J: *Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: exploratory analysis of the REAL-2 trial*. Annals of Oncology, 2016; 27: 687-92.

27. Kubo T, Ono S Ueno H, Shinto E, Yamamoto J Hase K: *Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma*. Int J Colorectal Dis, 2014; 29:1091-1099.

28. Balkwill F, Mantovani A: *Inflammation and cancer: Back to Virchow?* Lancet, 2001; 357:539-45.