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The relationship between systemic immune-inflammation indexes and treatment response in locally advanced esophageal cancer

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ABSTRACT

Aim: Systemic immune-inflammation indexes have been reported to be associated with clinical outcomes in several malignancies. Herein, we aimed to evaluate the potential relationship between prognostic nutritional index (PNI), systemic immune-inflammation index (SII), the neutrophil- to- lymphocyte ratio (NLR), the monocyte- to- lymphocyte ratio (MLR), the platelet-to-lymphocyte ratio (PLR) and the treatment response in patients with esophageal cancer who underwent neoadjuvant chemoradiotherapy (CRT).

Material and Method: Esophageal cancer (EC) patients who underwent neoadjuvant CRT were retrospectively enrolled in the study. Immune-inflammation indexes were calculated from pretreatment blood counts in samples obtained. The relationships between PNI, SII, NLR, MLR, PLR values, treatment response, and overall survival (OS) rates were examined.

Results: The data of 103 patients with EC who were referred to the Radiation Oncology Clinic of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were retrospectively analyzed. In the univariate analysis for OS, alcohol consumption, CRT agent, NLR, MLR, PLR, SII and PNI were found as prognostic factors. Also alcohol consumption was found as an independent prognostic factor in multivariate analyzes (HR:5.201, 95% CI:1.9-14.2, p=0.01).

Conclusion: In our study, high SII and low PNI values were not found to be independent poor prognostic factors for OS, but lower OS rates were observed in patients with high SII and low PNI values.

Keywords: Esophageal cancer, treatment response, systemic immune-inflammation index

INTRODUCTION

Esophageal cancer (EC) is the sixth leading cause of death and 8th most common cancer worldwide (1). Most common subtype is squamous cell cancer (SCC). Use of tobacco products, alcohol and nitrosamines are risk factors for esophageal SCC. Obesity, Barrett's esophagus, gastroesophageal reflux disease and use of tobacco products are important risk factors for esophageal adenocarcinoma (EAC) (2). Diagnosis at an early stage is very important. While surgery alone is sufficient for the treatment of early-stage tumors, multidisciplinary treatment options are preferred in locally advanced disease. Prognosis of advanced disease is poor. Although modalities such as radiotherapy (RT), chemotherapy (CT) and surgery are being used in combination in the treatment of esophageal cancer, its prognosis is unfortunately poor with five-year overall survival (OS) rates ranging between 15% and 25% (3). In patients with borderline resectable locally advanced esophageal cancer, preoperative chemoradiotherapy (CRT) followed by surgery is the most commonly used treatment modality. In the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), patients were randomized to preoperative RT and concurrent weekly CT followed by surgery or surgery alone, and it was reported that OS was significantly increased in the CRT arm with a median 7-year follow-up with similar complication rates (4). In the study of Donohoe at al. (5) pathological complete response was observed in less than 30 % of the patients with EC who underwent neoadjuvant CRT. In another study, survival benefit was reported in patients who had complete response to treatment (6).

In recent years, increasing evidence has shown that inflammatory biomarkers are significantly associated with poor prognosis in EC. However, the detailed mechanisms still remain unclear. There are possible explanations for the

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association between inflammatory biomarkers and poor prognosis in patients with solid tumors. Firstly, neutrophils promote proliferation of tumor cells by producing proteolytic enzymes including matrix metalloproteinases (MMPs) and serine proteases, and stimulate both tumor angiogenesis by releasing proangiogenic factors including MMP 9 and vascular endothelial growth factor (VEGF). Neutrophils cause local immunosuppression by disrupting T-cell responses and inducing T-cell death (7-10). Secondly, there is increasing evidence that T-lymphocytes play a critical anti-tumor role by inhibiting tumor cell proliferation and metastasis, inducing cytotoxic cell death, and promoting antitumor immune responses (11). Thirdly, platelets interact directly with tumor cells and release factors that promote tumor growth, invasion and angiogenesis (12). Platelets can contribute to metastasis by stabilizing tumor cell arrest in the vasculer system, stimulating tumor cell proliferation, and promoting extravasation of tumor cells (13). Recently, it has become important for clinicians to foresee patients that will respond to treatment and to devise an individualized treatment plan.

In our study, we aimed to investigate the relationship between pretreatment inflammatory parameters such as NLR, MLR, PLR, SII and PNI, and response to treatment and survival in patients with esophageal cancer who had undergone neoadjuvant chemoradiotherapy.

MATERIAL AND METHOD

This study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date:26.05.2022, Decision No: 2022-05/109). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This analysis was conducted in 103 patients with EC who underwent neoadjuvant chemoradiotherapy (CRT) in our clinic from January 2014 to January 2022. Staging was done using the 8th Edition American Joint Committee on Cancer TNM Staging Manual guidelines (14). Histologically confirmed EC patients with Eastern Cooperative Oncology Group (ECOG) performance status scores between 0 and 2 were included in the study. Patients with active concomitant infection, distant metastases at the time of diagnosis, autoimmune diseases, hematological diseases, missing baseline blood test results and corticosteroid users during treatment were not included in the study. Data related to clinicopathological variables such as gender, age, tumor localization,and pathology, smoking status, alcohol consumption, were obtained by retrieving medical records. All patients had neoadjuvant concurrent CRT (chemotherapy including paclitaxel (50 mg/m²)-carboplatin (AUC 2) and fluorouracil (750-1000 mg/m²) and cisplatin (75-100 mg/m²) and a daily radiotherapy dose of 1.8/2 Gy amounting to a total dose of 41.4-54 Gy delivered using intensity modulated radiotherapy (IMRT). IMRT was planned using Eclipse (ver. 11: Varian Medical Systems, Inc. Palo Alto, CA, USA) planning software. To evaluate the response to neoadjuvant treatment all patients underwent restaging 4-6 weeks after the completion of CRT. Immune-inflammatory factors were obtained from pretreatment values and immune-inflammation indexes were calculated. The PNI was calculated using the formula:serum albumin (g/dl) + 5 x absolute lymphocyte count. The neutrophil (N; $\times10^9$/l) to lymphocyte (L; $\times10^9$/l) ratio (NLR) was calculated by dividing the absolute neutrophil counts by absolute lymphocyte counts. The monocyte (M; $\times10^9$/l) lymphocyte ratio (MLR) was calculated by dividing the absolute monocyte counts by absolute lymphocyte counts. The platelet (P; $\times10^9$/l) lymphocyte ratio (PLR) was calculated by dividing the absolute platelet counts by absolute lymphocyte counts. SII was estimated using the formula: platelet counts x neutrophil counts/lymphocyte counts (15-17).

Treatment response was evaluated using histopathology reports in patients who were surgically treated and using Response Evaluation Criteria in Solid Tumors (RECIST) criteria in patients who were not surgically treated. The categories were defined as complete response, partial response, stable disease and progresive disease (18). The relationship between PNI, NLR, MLR, PLR, SII values and treatment response-OS were evaluated statistically. We defined OS as the time from the histopathologic diagnosis of EC to the last follow-up or death.

Statistical Analysis

The statistical analysis was performed using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) Version 22 software package. The descriptive categorical data were expressed as numbers (n) and percentage values (%) while descriptive continuous data were presented as mean±standard deviation (mean±SD). Chi-Square test was applied for intergroup comparisons of categorical variables. The fitness of continuous variables to normal distribution was evaluated by Kolmogorov-Smirnov test. In intetrgroup comparisons. Student-t test was used for normally distributed variables while Mann-Whitney U test was applied for non-normally distributed variables. In intergroup comparisons One Way ANOVA test was used for variables with normal and Kruskal -Wallis test with non-normal distribution. Receiver operating characteristic (ROC) curve analysis was performed to analyze the area under the (ROC) curve and to determine optimal cut-off values. Kaplan-Meier method was used for univariate analysis of local control and survival. Multivariate Cox regression analysis that contained all the factors of univariate analysis was performed. The statistical significance level of the analyses was set at $p<0.05$.

RESULTS

A total of 103 patients with a median age of 60 years (range: 19-84 years) including 37 female (35.9 %) and 66 male (64.1%) cases diagnosed as esophageal carcinoma enrolled in this study, Most patients had a history of smoking (60.4%) and a few (5.1%) patients were alcohol users The indicated number of patients had ECOG performance status scores of 0 (n=27), 1 (n=72), and 3 (n=4) points.

Tumors were located proximally in 15, thoracically in 29 and distally in 59 patients. The majority of the cases (88.3%) had squamous cell carcinoma, and the rest adenocarcinoma. In addition, 87 (84.5%) patients had received paclitaxel-carboplatin, the others fluorouracil and cisplatin as concurrent chemotherapy. Fifty patients (48.5%) underwent surgery, 27 patients (26.2%) didn't undergo surgery and 26 patients (25.2%) didn't want to undergo surgery after neoadjuvant chemoradiotherapy. All patients had locally advanced disease. Patients were staged with PET-CT before initation of the treatment. Neoadjuvant treatment was planned for all patients. All patients received neoadjuvant concurrent chemoradiotherapy. Fifty patients (48.5%) underwent surgery 6-8 weeks after the completion of neoadjuvant treatment but 53 patients did not want surgery so had no operation.

The response rate was evaluated histopathologically in patients who had and radiologically in patients who had not unergone surgery . Complete, and partial response rates were observed in 54 (52.4%), and 28 (27.2%) patients, respectively. Twelve patients had no response and evaluated as stable disease. Nine patients had progressive disease. The relationship between PNI, NLR, MLR, PLR and SII values and treatment response was not statistically difference (p>0.005) (**Table 1**). In the univariate analysis for OS, alcohol consumption, CRT agent, NLR, MLR, PLR, SII and PNI were found that as prognostic factors. Also alcohol consumption was revealed as an independent prognostic factor in multivariate analyzes (HR:5.201, 95% CI:1.9-14.2, p=0.01). Although the p value was significant, the SII value was not considered significant because the confidence interval included 1.0. Gender, comorbidity, pathology, tumor localization, ECOG scores were not found to be associated with survival (**Table 2**).

In the univariate analysis 5 -year survival rates were %29.8 in patients with SII ≤ 604 and %9.7 in patients with SII>604 (p=0,003); 7.4% in patients with PNI ≤ 40 and 28.9% in patients with PNI > 40 (p=0.014) without any statistically significant difference as for 5-year survival rates. The findings are shown in **Figures 1a-1b**. When all patients were evaluated, the median follow up time, and average survival time were 15.5, and 31.5 months, respectively. While 2- year and 5- year survival rates were 38.8% and 16.9%, respectively.

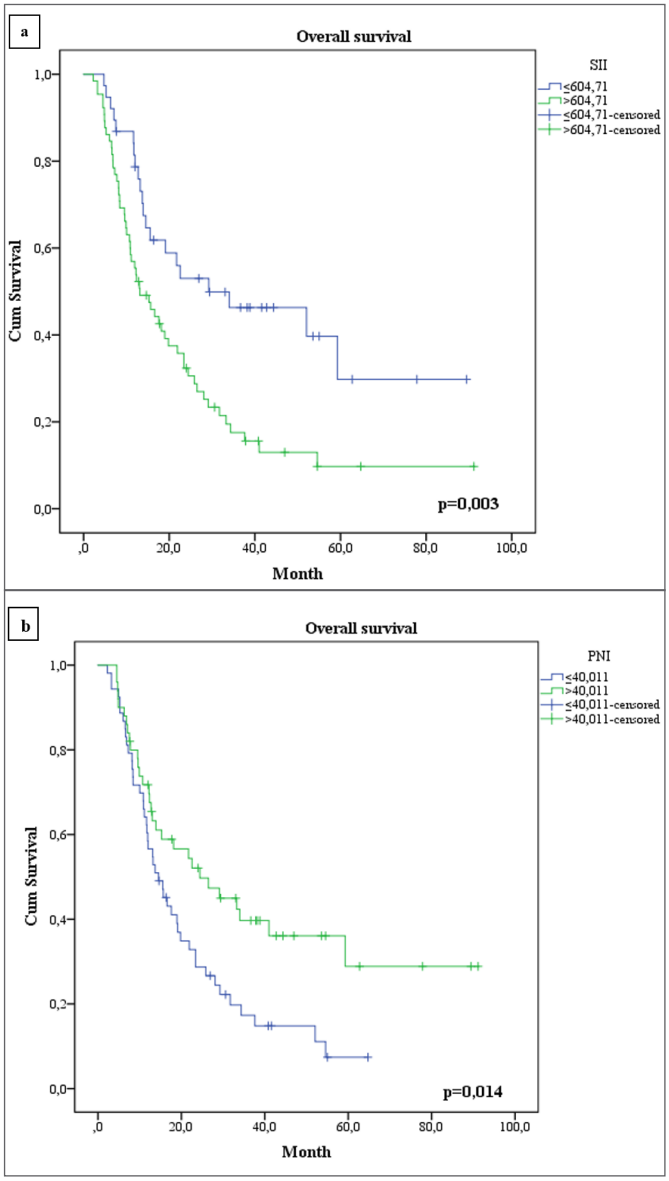

Figure 1. Kaplan-Meier survival curves for a SII and b PNI on survival overall.

Abbreviations: SII: Systemic immune-inflammation index, PNI: Prognostic nutritional index

Table 1. The relationship between NLR, MLR, PLR, SII and PNI values and. treatment response.

	Complete response	Partial response	Stable disease	Progressive disease	P value
NLR, mean±SD	3.4±3.1	3.4±1.5	2.9±.9	4.9±6.7	0.801*
MLR, mean±SD	.3±.2	.3±.1	.3±.1	.5±.6	0.561*
PLR, mean±SD	170.9±122.1	205.2±97.0	161.2±71.6	209.6±111.9	0.063*
SII, mean±SD	904.5±1182.2	1021.1±511.1	841.8±397.3	1200.3±1352.5	0.295*
PNI, mean±SD	38.6±55.3	37.0±54.3	39.9±58.9	36.6±68.4	0.558**

*Kruskal- Wallis analysis, **One Way ANOVA analysis Abbreviations: NLR: neutrophil- to- lymphocyte ratio, MLR: monocyte- to- lymphocyte ratio, PLR: platelet- to- lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index.

Table 2: Univariate and multivariate analysis of the prognostic factors affecting OS.

Univariate Analysis		**Patients n (%)**	**5-year OS (%)**	**Mean**	**Median**	**p-value**
Gender						0.131
	Female	37 (35.9)	24.3	38.3±6.0	19.1	
	Male	66 (64.1)	14.7	28.0±3.9	15.5	
Alcohol consumption						0.002
	Present	5 (5.1)	N/A	8.7±3.9	4.8	
	Absent	93 (94.9)	17.9	32.3±3.5	16.6	
Comorbidity						0.732
	Absent	36 (35.0)	11.7	31.7±5.5	18.9	
	Present	67 (65.0)	18.9	30.8±4.0	16.6	
Pathology						0.752
	SCC	91 (88.3)	16	30.8±3.5	17.6	
	Adenocarcinoma	12 (11.7)	20	34.3±10.3	7.6	
Tumor localization						0.270
	Proximal location	15 (14.6)	14.8	25.6±6.1	18.9	
	Thoracic location	29 (28.2)	NR	22.9±3.9	15.2	
	Distal location	59 (57.3)	23.3	35.9±4.7	21.9	
ECOG						0.137
	0	27 (26.2)	12.8	25.7±5.7	12.7	
	1	72 (69.9)	12.5	28.9±3.2	18.1	
	2	4 (3.9)	50	42.9±11.2	29.1	
CRT agent						0.048
	paclitaxel-carboplatin	87 (84.5)	23	35.1±3.9	21.7	
	fluorouracil and cisplatin	16 (15.5)	NR	18.1±3.5	12.3	
NLR						0.023
	≤2.99	53 (51.5)	23.7	38.2±5.1	21.9	
	>2.99	50 (48.5)	11	24.8±3.9	13	
MLR						0.018
	≤0.32	69 (67.0)	21.3	35.9±4.2	22.5	
	>0.32	34 (33.0)	7.7	19.2±3.1	11.1	
PLR						0.022
	≤121.66	23 (22.3)	NR	34.9±4.2	34	
	>121.66	80 (77.7)	14.5	27.8±3.4	14.5	
SII						0.003
	≤604.71	38 (36.9)	29.8	44.1±6.2	29.2	
	>604.71	65 (63.1)	9.7	24.1±3.4	13.1	
PNI						0.014
	≤40.011	53 (51.5)	7.4	21.5±2.6	14.6	
	>40.011	50 (48.5)	28.9	40.9±5.5	24.4	
Multivariate Analysis		**Hazard ratio**		**95% CI**		**p-value**
Alcohol consumption	Present vs Absent	5.201		1.900-14.238		0.001
CRT agent	Paclitaxel-carboplatin vs fluorouracil and cisplatin	1.738		.969-3.117		0.064
NLR	≤2.99 vs >2.99	.717		.349-1.475		0.366
MLR	≤0.32 vs >0.32	1.428		.818-2.494		0.210
PLR	≤121.66 vs >121.66	1.273		.589-2.749		0.539
SII	≤604.71 vs >604.71	1.900		.846-4.267		0.120
PNI	≤40.011 vs >40.011	.636		.379-1.067		0.087

Abbreviations: OS: overall survival, ECOG: Eastern Cooperative Oncology Group, CRT: chemoradiotherapy, NLR: neutrophil- to- lymphocyte ratio, MLR: monocyte- to-lymphocyte ratio, PLR: platelet- to- lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index, CI: confidence interval, N/A: not available.

DISCUSSION

The varied response in EC patients after neoadjuvant CRT is a serious challenge for administration of appropriate treatment to these patients. The prediction of the prognosis is very important for the management of treatment for EC. There are various pre- and post -treatment parameters in the literature. Chen et al. (16) determined a systemic inflammation parameter, namely systemic immune-inflammation index (SII), which is a predictor for OS and recurrence of colorectal cancer. Gao et al. (17) reported that the SII is an independent prognostic factor in patients with surgically resected esophageal SCC. Prognostic nutritional index (PNI) was used by Buzby et al. (19) in 1980 to estimate operative risk after gastrointestinal surgery. Onodera et al. (20) developed PNI to predict postoperative morbidity and mortality in patients undergoing gastrointestinal surgery.

In recent studies, a relationship between inflammation and disease survival with parameters as NLR, PLR, SII and PNI has been shown, but there is no consensus on the cut-off values of these parameters yet. Fu et al (21) evaluated the prognostic significance of preoperative systemic inflammation index score (SIS), calculated by a composite score of the lymphocyte-to-monocyte ratio and the albumin content in serum, in patients with esophageal SCC and reported that the optimal cut-off values for preoperative NLR, LMR and albumin were 2.27, 3.79 and 36.55, respectively. Univariate analyses found that NLR, LMR, albumin and SIS were significantly associated with OS. The authors found that SIS was an independent prognostic factor. Cai et al. (22) aimed to analyze the association of hematologic markers with prognosis and toxicities in patients with locally advanced esophageal SCC who underwent neoadjuvant CRT. They also reported that patients with high SII (≥583.45), PLR (≥142.17) and NLR (≥2.77) had significantly worse prognosis and severe adverse events. One of the inflammation indexes is platelet/lymphocyte ratio (PLR). Asher et al. (23) found that median OS in patients with a PLR of <300 was 37.4 months (95% CI 26.1-48.7) and 14.5 months (95% CI 11.7-17.2) in patients with a PLR of > 300. They have shown that PLR is a novel independent prognostic marker in patients with ovarian cancer. Hirahara et al. (24) retrospectively analyzed data from 169 patients who underwent radical esophagectomy and found that patients with low PNI had significantly worse OS than that of the patients with a high PNI (HR 2.612; 95% CI 1.600–4.405). In this study, PNIs <49.2 (HR 3.887) were determined as independent adverse predictive factors for cancer specific-survival.

In a study, the researchers found that pre-CRT NLR, pre-CRT PLR, absolute lymphocyte counts estimated during CRT, post-CRT platelet counts and post-CRT PLR were significantly associated with complete response in esophageal SCC patients after neoadjuvant CRT. They demostrated that pre-CRT NLR, post-CRT PLR were independent predictors of complete response contrary top re-CRT PLR (25). We observed no relationship between treatment response and NLR, PLR values. Koh et al. (26) evaluated LMR, NLR and PLR before and after definitive concurrent CRT in esophageal SCC patients. They reported that post-CRT NLR predicted OS better than the other above mentioned parameters. In their study the median follow up time was 11.4 months, and the OS rates at 1 and 3 years were 48.5% and 21.6%, respectively. However, in our study, cut-off values of NLR (2.99), PLR (121.66), SII (604.71), and PNI (40) for OS were as indicated. In our study, lower survival rates were observed in patients with higer NLR, SII and lower PLR and PNI values. In recent studies varying survival rates have been reported in patients with locally advanced esophageal SCC. In a review Herskovic et al. (27) reported that 3- and 5-year- OS rates ranged between 19.2%-32 % and 33%-39% for locally advanced esophageal cancer patients treated with concurrent CRT followed by surgery, respectively. Yang et al. (28) compared the treatment efficacy of neoadjuvant CRT plus surgery with surgery alone among patients with locally advanced esophageal cancer. They reported respective 3-, and 5-year- OS rates as 65.8% and 59.9% in the neoadjuvant CRT group compared with corresponding OS rates of 57.8% and 49.1% in the surgery group. In our study 2-, and 5-year survival rates were 38.8% and 16.9%, respectively.

Our study have some limitations as being a single-center retrospective trial performed in small number of heterogeneous patient population. So conduction of multicenter prospective studies will be needed to evaluate these findings.

CONCLUSION

Pretreatment immune-inflammation indexes including PNI and SII may be potentially effective prognostic factors in locally advanced EC patients who underwent neoadjuvant chemoradiotherapy. In this study, however, higher SII and lower PNI values were not found to be independent adverse prognostic factors for OS, however lower OS rates were detected in patients with comparatively higher SII and lower PNI values.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date:26.05.2022, Decision No: 2022-05/109).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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