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The Correlation of Systemic Immune-Inflammation Index and Neutrophil to Lymphocyte Ratio with the Histopathological Findings in Patients with Tongue Cancer

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Abstract

Introduction: The aim of this study is to evaluate the correlation of the systemic immune-inflammation index (SII) and neutrophil to lymphocyte ratio (NLR) with the histopathological findings in the patients with tongue squamous cell carcinoma (SCC).

Methods: The aim of this study is to evaluate the correlation of the systemic immune-inflammation index (SII) and neutrophil to lymphocyte ratio (NLR) with the histopathological findings in the patients with tongue squamous cell carcinoma (SCC).

Results: The comparison of tongue SCC group with healthy subjects revealed statistically significant higher NLR, and SII (p=0.027, p=0.023 respectively). ROC curve analysis indicated the optimal NLR and SII cut-off values as 1.98, 477.30 respectively. The comparisons of perineural invasion, lymphovascular invasion, and extranodal extension with SII were statistically significant (p=0.044, p=0.012, p=0.022). Nevertheless, NLR was only correlated with the extranodal extension (p=0.003). There was no significant correlation between the pathological degree of the tongue SCC neither with NLR nor SII.

Discussion and Conclusion: The systemic immune-inflammation index is a novel, inexpensive and useful biomarker which has a predictive value in the disease progression of tongue SCC patients. High levels of pretreatment SII indicate a probable high risk of perineural and/or lymphovascular invasion, and extranodal extension.

Keywords: Neutrophil to lymphocyte ratio; systemic immune-inflammation index; tongue squamous cell carcinoma.

Lip and oral cavity cancer is the 15th most common cancer in Europe with around 61.400 new cases diagnosed in 2012 [1]. Every year 270000 new oral cavity cancer cases have been diagnosed around the world [2]. The socioeconomic status and poverty are associated with oral cavity cancer, and the incidence is higher in the most disadvantaged population [3]. In 2008, Lambert et al. have shown that vast majority of the world's 260 000 newly diagnosed oral cavitary cancer patients were living in developing countries. This type of cancer occurs more commonly in men than in women. The etiology is multifactorial, and the leading etiological factors are smoking, tobacco chewing and intensive alcohol usage [2].

Tongue cancers are the second most common site of all oral cavity cancers after lip cancer, while they are the most common site for intraoral cancers with a rate of about 50% [2]. Approximately 90% of the tongue cancers are squamous cell carcinomas and uncommonly minor salivary gland tumors, lymphomas, melanomas, metastatic tumors, and sarcomas could be seen [4].

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The new American Joint Committee on Cancer (AJCC) staging manual (8th edition) allows a better stratification of oral SCC patients by including the depth of invasion and extranodal extension which reflects a worse disease-free and overall survival [5]. There are also other adverse pathologic features that are effective on prognosis such as perineural invasion and lymphovascular invasion [6].

The relation between inflammation and tumor progression has been known for many years. The tumor microenvironment is largely organized by inflammatory cells and these cells are essential in the proliferation, invasion, and metastasis of neoplasms [7]. The laboratory studies have shown that tumor cells may release cytokines that stimulate the recruitment of the neutrophils. Within the tumor microenvironment, neutrophils can release cytokines to proliferate tumor cells, trigger immunosuppression and promote tumor angiogenesis [8, 9].

According to the literature, the relation of tumor progression with inflammatory parameters such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) has been shown in different studies [10-13]. In recent studies, the relation of higher levels of SII with poor prognosis have been revealed in many solid tumors, such as hepatocellular carcinoma [14] small cell lung cancer [15], esophageal squamous cell cancer [16], renal cell carcinoma [17] colorectal cancer [18], and nasopharyngeal cancer [19]. To the best of our knowledge, the predictive value of SII in tongue SCC and the correlation of inflammatory biomarkers with perineural invasion, lymphovascular invasion, extranodal extension, and pathological differentiation degree have not been reported before.

In this study, we aimed to evaluate the correlation of NLR and SII which based on neutrophil, lymphocyte and platelet counts with the histopathological findings in patients with tongue SCC. The presence of perineural invasion, the presence of lymphovascular invasion, extranodal extension, and pathological differentiation degree were used to show up the probable relationship of histopathologic findings with NLR and SII.

Materials and Methods

Patient Selection: This study was performed in the Otolaryngology Department of Health Science University Umraniye Education and Research Hospital. The retrospective study protocol was approved by the Research Ethical Committee of the Umraniye Education and Research Hospital.

Thirty-three (18 male, 15 female) patients operated and followed up between January 2008 and February 2018 for tongue SCC were retrospectively reviewed. The patients with Tongue SCC in every stage were enrolled in the study and all parameters that calculated in the study were obtained from their preoperative complete blood counts (CBC). In this study, CBC parameters of neutrophil, lymphocyte, and platelet counts were recorded. The systemic immune-inflammation index which is a novel inflammatory index was calculated by using neutrophil (N), lymphocyte (L) and platelet (P) counts (NxP/L). The presence of perineural and lymphovascular invasion, extranodal extension, and pathological differentiation degree of the patients was recorded. These features compared with SII.

Thirty-four (17 male, 17 female) randomly selected age- and sex-matched healthy individuals whose CBCs were done for regular checkups comprised the control group.

Exclusion Criteria: Patients who had an evidence of a heart disease (such as congestive heart failure, valvular heart disease, myocardial infarction), autoimmune disease (such as Hashimoto Thyroiditis, Behçet's Disease) or suffered from an acute infection (patients with elevated white blood cell (WBC) count (>12,000/mL) or neutrophil (>70%)), hematological diseases (patients with increased hemoglobin (>18gr/dL) or decreased hemoglobin (<12gr/dL) and other diseases such as sickle cell anemia, coagulopathies (such as Factor V Leiden mutation), and the patients who have distant metastasis were excluded.

Biochemical and Hematological Analyses

Complete blood count was evaluated using peripheral venous blood samples obtained from the preoperative period. CBC testing was performed using an automated hematology analyzer (CELL-DYN 3700, Abbott, USA) initial to the treatment. The neutrophil, lymphocyte, and platelet counts were recorded and the SII was calculated from these parameters.

Statistical Analysis

Statistical analysis was performed by SPSS 20.0 (IBM Corporation, New York, NY) program. In addition to standard descriptive statistical calculations (mean, median, and standard deviation), qualitative parameters showing normal distribution were compared with the independent sample t-test, and parameters showing abnormal distribution were compared with the Mann-Whitney U test. Fisher Exact Test was used for the comparison of the sex. Kolmogorov-Smirnov test was used to analyze the homogeneity of variance. To analyze the qualitative data Pearson chi-square or Fisher's exact tests were used. In all tests, $p<0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) curve was calculated to determine the optimal NLR and SII cut-off values.

Results

The distribution of the demographic data of study and control groups is shown in table 1. The mean ages of patient and control groups were 59.09±14.31 and 55.58±6.93 years, respectively. The male-to-female ratios of these groups were 18:15 and 17:17, respectively. The mean follow-up period of the cancer patients was 25.81±23.50 months.

The mean±standard deviation of NLR and SII of the tongue SCC and control groups were compared in table 2. As presented in table 2 NLR and SII of patients with tongue SCC were significantly different from the control group (p=0.027, p=0.023 respectively).

Receiver operating characteristic analysis indicated the optimal NLR and SII cut-off values. We selected the cut-off point of NLR as 1.98 and divided all cancer patients into either high (>1.98) or low (≤1.98) NLR groups and analyzed the correlation of NLR with perineural invasion, lymphovascular invasion, extranodal extension according to this value. Additionally, same ROC curve analysis was calculated for SII, and the selected cut-off value was 477.30 for SII. Patients also divided into either high (>477.30) and low (≤477.30) SII groups for perineural and lymphovascular invasion. On the other hand the cut-off value of SII for extranodal extension was found as 509.26. The ROC curve graphics of lymphovascular invasion, perineural invasion and extranodal extension for NLR and SII were demonstrated in figure 1, 2 and 3.

The comparison of perineural and lymphovascular invasion positivity with NLR and SII were demonstrated in table 3. The presence of perineural invasion and lymphovascular invasion were more frequently revealed in the patients with higher values of SII (p=0.044 for perineural invasion, p=0.012 for lymphovascular invasion). However, higher values of NLR statistically did not correlate with the presence of perineural or lymphovascular invasion either (p>0.05).

The correlations of NLR and SII with extranodal extension in patients with tongue SCC were demonstrated in table 4. The extranodal extension was statistically significantly correlated with NLR and SII (p=0.003, p=0.022 respectively).

The pathological differentiation degree of the tongue SCC was compared with NLR and SII in table 5. There was no significant correlation between the pathological degree of the tongue SCC and neither the NLR nor SII values (p>0.05).

Table 1. Demographic parameters of groups

	Tongue SCC.	Control	p
Number of subjects	33	34	
Sex (M/F); *n*	18/15	17/17	[a]0.710
Age *(year)*			
Mean±SD	59.09±14.31	55.58±6.93	[b]0.205
Median (Range)	59 (28-87)	55 (47-73)	
Follow-up *(month)*			
Mean±SD	25.81±23.50		
Median (Range)	24 (1-99)		

[a]Fisher Exact Test; [b]Independent Sample t Test; *p<0.05.

Table 2. The comparison of the mean±standard deviation and median of NLR and SII parameters of the tongue SCC and control groups

Parameters	Tongue SCC n:33	Control n:34	p
NLR			
Mean ± Std. Dev	2.25±0.97	1.77±0.74	
Median	2.05	1.81	[a]0.027*
(Min-Max)	(0.80-5.99)	(0.65-4.79)	
SII			
Mean±Std. Dev	573.32±264.54	448.50±163.23	
Median	537.15	475.97	[a]<0.023*
(Min-Max)	(170.53-1268.47)	(174.40-681.10)	

[a]Independent Sample t -Test; *p<0.05.

Discussion

The intimate relation between cancer and inflammation has been studied, and the effects of inflammatory cells in carcinogenesis have been revealed widely. Tumor microen-

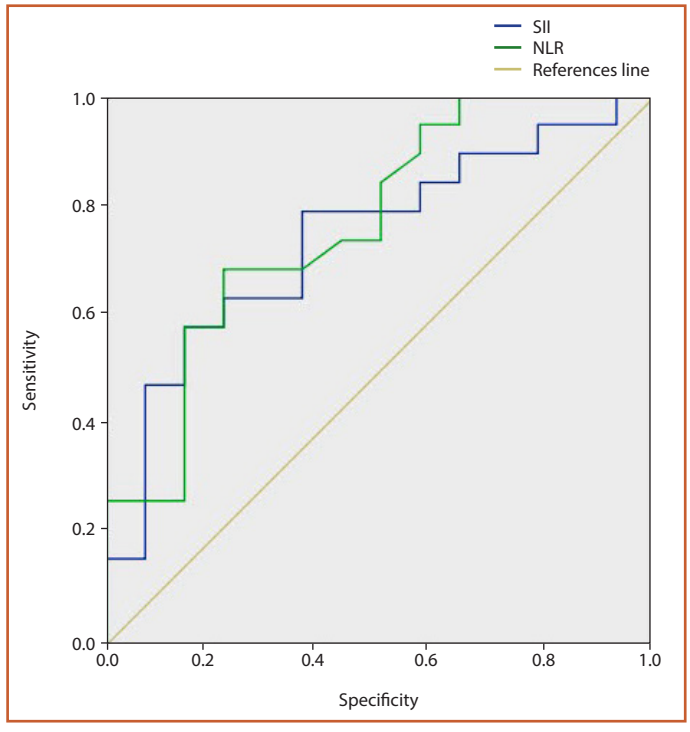

Figure 1. The ROC curve analysis of lymphovascular invasion for NLR and SII.

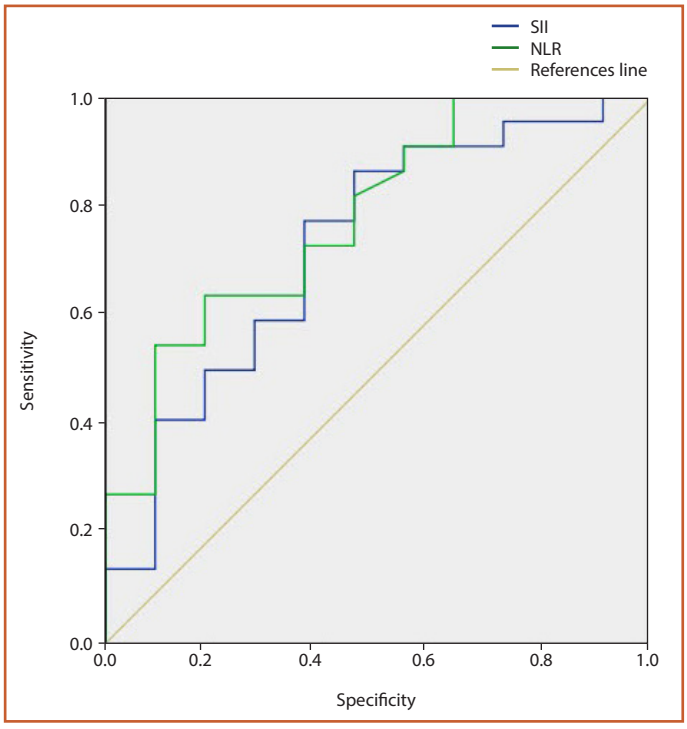

Figure 2. The ROC curve analysis of perineural invasion for NLR and SII.

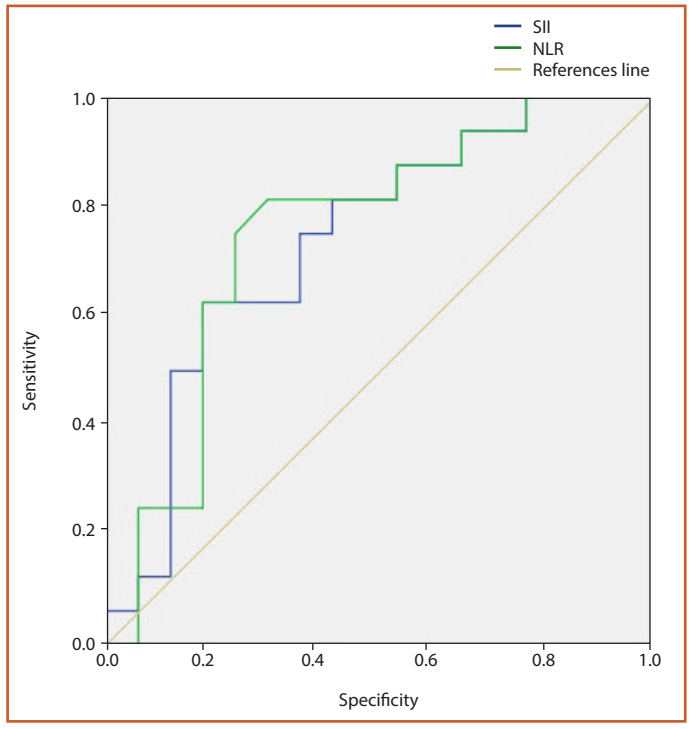

Figure 3. The ROC curve analysis of extranodal extension for NLR and SII.

vironment which organized by inflammatory processes leads to tumor angiogenesis, invasion, and metastasis [7]. Neutrophils activate tumor growth by producing proangiogenic factors such as vascular endothelial growth factor, proteases, and chemokines, and they enhance adhesion of circulating tumor cell in distant sites [20, 21]. Also, platelets and coagulation system have an important role in the progression of cancer facilitating the tumor cell adhesion to the endothelium and preventing cell death [22].

Lymphocytes inhibit proliferation of tumor cells and restrain metastasis by cytokine production and inducing cytotoxic cell death [23]. Therefore, low levels of circulating lymphocytes might also lead to substantial immune effects on cancerous cells and facilitate cancer cell invasion and metastasis [24]. In previous studies, it has been shown that decreased lymphocyte count is an independent prognostic factor for overall and progression-free survival in several cancers [25].

In recent studies, a novel prognostic marker, SII has been investigated in various malignancies, and the correlation of SII, NLR, lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been shown in many cancer types [14-18, 26]. High levels of neutrophils and platelets with low levels of lymphocytes cause higher SII which may give rise to a stronger inflammatory and a weaker immune response in cancer patients. Elevated SII is associated with a worse overall survival in many solid tumors [26]. Although the prognostic value of SII has been reported in different cancer types, the relation of SII with tongue SCC has not been studied before. Therefore, in this study, we investi-

Table 3. The correlation of NLR and SII with the presence of perineural and lymphovascular invasion in patients with tongue SCC

	Perineural Invasion n:33		p	Lymphovascular Invasion n:33		p
	Positive	Negative		Positive	Negative	
SII≤477.30	6	7	[a]0.044*	4	9	[a]0.012*
SII>477.30	16	4		15	5	
NLR≤1.98	8	7	[a]0.138	4	7	[a]0.081
NLR>1.98	14	4		15	7	

[a]Pearson Chi-Square test; *p<0.05.

Table 4. The correlation of NLR and SII with extranodal extension (ENE) in patients with tongue SCC

	ENE n:33		p
	Positive	Negative	
SII≤509.26	4	11	[a]0.022*
SII>509.26	12	6	
NLR≤1.98	3	12	[a]0.003*
NLR>1.98	13	5	

[a]Pearson Chi-Square test; *p<0.05.

gated the SII values in patients with tongue SCC. In addition, we demonstrated statistically higher values of SII in cancer patients than healthy subjects.

Pretreatment C-reactive protein (CRP) levels, leucocytes, monocytes, lymphocytes, neutrophils, basophils, eosinophils, platelets, NLR, derived NLR (dNLR), LMR, and PLR obtained from the peripheral blood were analyzed in oral SCC by Grimm et al. in a study [13]. The ROC analysis determined cut-off values for CRP levels, leucocytes, monocytes, lymphocytes, neutrophils, NLR, dNLR, LMR, PLR which showed significant differences between the oral SCC and control groups. Also, NLR was significantly directly correlated with PLR, and LMR was significantly inversely associated with NLR and PLR.

Ong et al. studied WBC count in early tongue SCC and revealed that low pretreatment LMR and high PLR indicate poor survival in these patients [10]. Likewise, Ozturk et al. [12] studied the predictive value of preoperative NLR, PLR, and SII in local recurrence and survival in the patients operated for early stage tongue SCC and the relationship between NLR, PLR, SII and local recurrence was significantly correlated according to the cut-off values whereas the usability of NLR, PLR, and SII in overall and disease-free survival was limited.

Park et al. [27] presented the association of LMR with T classification, N classification, and pathologic stage, NLR with T classification and pathologic stage, and PLR with N classification and pathologic stage in oral cancer patients. They described prognostic score system based on these three ratios and demonstrated a significant association of these ratios with the disease-specific survival of oral cancer patients who received surgery. The presences of perineural invasion and lymphovascular invasion have a significant prognostic value [6]. Perineural invasion is correlated with nodal status and T stage and is related to disease-free survival. In this study, we also analyzed the relationship between the SII and the presence of perineural and lymphovascular invasion, and advanced pathological differentiation status which are important determinants of cancer prognosis. The presence of perineural invasion and/or lymphovascular invasion are frequently revealed in the patients with higher values of SII, and higher SII values were significantly related to the poor pathological differentiation of the tongue SCC.

Conclusion

The systemic immune-inflammation index might be helpful to show the clinical course of the cancer patients. High pretreatment SII indicates possible increased perineural and/or lymphovascular invasion positivity, and presence of extranodal extension. Therefore, we suggest close follow-up for patients with high NLR and SII.

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Conflict of Interest: None declared.

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Table 5. The correlation of NLR and SII with pathological differentiation degree of tongue SCC

Parameters	Well n:8	Moderate n:22	Poor n:3	p
N/L				
Mean±SD	2.25±0.80	2.29±1.09	1.94±0.54	
Median	2.42	1.98	1.64	[a]0.797
(Min-Max)	(0.80-3.40)	(1.07-5.99)	(1.61-2.57)	
SII				
Mean±SD	631.95±258.33	573.87±278.71	413.01±134.97	
Median	667.32	513.21	348.75	[a]0.355
(Min-Max)	(170.53-924.85)	(223.46-1268.47)	(322.17-568.11)	

[a]Kruskal Wallis Test; *p<0.05.

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