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ORIGINAL ARTICLE

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

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Abstract

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

Methods: 33 patients with tongue SCC were enrolled. The SII (NxP/L) based on neutrophil (N), lymphocyte (L), and platelet (P) counts was used as a biomarker. The results were compared with those of 34 healthy individuals. In addition, the correlation of NLR and SII with the presence of perineural and lymphovascular invasion, extranodal extension, and pathological differentiation degree was studied.

Results: Patients with tongue SCC had significantly higher NLR and SII than healthy subjects (p=0.027, p=0.023 respectively). Receiver operating characteristic curve analysis indicated optimal NLR and SII cut-off values to be 1.98 and 477.30, respectively. 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 only correlated with extranodal extension (p=0.003). No significant correlation was observed between the pathological degree of tongue SCC and NLR and SII.

Discussion and Conclusion: SII is a novel, inexpensive, and useful biomarker that has a predictive value in the disease progression of patients with tongue SCC. 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 cancers are the 15th most common cancers in Europe with around 61.400 new cases diagnosed in 2012 [1]. Every year 270.000 new oral cavity cancer cases are diagnosed worldwide [2]. 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. [2] have shown that the vast majority of the world's 260.000 newly diagnosed patients with oral cavity cancer were living in developing countries. This type of cancer more commonly occurs in men than in women. The etiology is multifactorial, and the leading etiological factors are smoking, tobacco chewing, and intensive alcohol usage.

Tongue cancers are the second most common of all oral cavity cancers after lip cancer, and these are the most common intraoral cancers with a rate of approximately 50% [2]. Approximately 90% of tongue cancers are squamous cell carcinomas (SCCs) and uncommonly minor salivary gland tumors, lymphomas, melanomas, metastatic tumors, and sarcomas are observed [4].

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The new American Joint Committee on Cancer staging manual (8th edition) allows a better stratification of patients with oral SCC by including the depth of invasion and extranodal extension, which reflects 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 relationship between inflammation and tumor progression has been known for several years. The tumor microenvironment is largely organized by inflammatory cells, and these cells are essential in the proliferation, invasion, and metastasis of neoplasms [7]. Laboratory studies have shown that tumor cells may release cytokines that stimulate the recruitment of 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 relationship between tumor progression and 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 relationship between higher levels of systemic immune-inflammation index (SII) and poor prognosis has been revealed in 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 correlation of inflammatory biomarkers with perineural invasion, lymphovascular invasion, extranodal extension, and pathological differentiation degree have not been reported before.

This study aimed to evaluate the correlation of NLR and SII based on neutrophil (N), lymphocyte (L), and platelet (P) counts with histopathological findings in patients with tongue SCC. The presence of perineural invasion, lymphovascular invasion, extranodal extension, and pathological differentiation degree were used to reveal the probable relationship between histopathological findings and NLR and SII.

Materials and Methods

Patient Selection

This retrospective study was conducted at the Otolaryngology Department of Health Science University Umraniye Education and Research Hospital, and the protocol was approved by the Research Ethical Committee of the Umraniye Education and Research Hospital.

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

Thirty-four (17 male, 17 female) randomly selected healthy individuals with matching age and sex, whose CBCs were evaluated during regular checkups, comprised the control group.

Exclusion Criteria

Patients with an evidence of heart (such as congestive heart failure, valvular heart disease, or myocardial infarction) or autoimmune (such as Hashimoto thyroiditis or Behçet's disease) diseases or those who suffered from an acute infection [patients with an elevated white blood cell (WBC) count (>12.000/mL) or N count (>70%)]; hematological diseases (patients with increased (>18gr/dL) or decreased (<12gr/dL) hemoglobin level]; and other diseases such as sickle cell anemia and coagulopathies (such as Factor V Leiden mutation) and those with distant metastases were excluded.

Biochemical and Hematological Analyses

CBC was evaluated using peripheral venous blood samples obtained from the preoperative period. CBC testing was conducted using an automated hematology analyzer (CELL-DYN 3700, Abbott, USA) prior to the treatment. N, L, and P counts were recorded, and SII was calculated from these parameters.

Statistical Analysis

Statistical analysis was conducted using 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 using independent sample t-test, and whereas those showing non-normal distribution were compared using Mann–Whitney U test. Fisher's exact test was used for the comparison of sex. Kolmogorov–Smirnov test was used to analyze the homogeneity of variance. Pearson's chi-square or Fisher's exact test was used to analyze qualitative data. $P<0.05$ was considered statistically significant.

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

Results

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

Table 2 shows the comparison of mean±standard deviation of NLR and SII between the patient and control groups. As presented in Table 2, NLR and SII of patients with tongue SCC were significantly different from those of the control group (p=0.027, p=0.023 respectively).

ROC curve analysis indicated the optimal NLR and SII cut-off values. Cut-off value of NLR was selected as 1.98, and all cancer patients were divided into either high (>1.98) or low (≤1.98) NLR groups; the correlation of NLR with perineural invasion, lymphovascular invasion, and extranodal extension was then analyzed as per this value. Additionally, the same ROC curve analysis was calculated for SII, and the selected cut-off value was 477.30, and patients were divided into either high (>477.30) or low (≤477.30) SII groups. for perineural and lymphovascular invasion. On the other hand, the cut-off value of SII for extranodal extension was calculated

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's exact test; [b]Independent sample t-test; *p<0.05.

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

Parameters	Tongue SCC n=33	Control n=34	p
NLR			
Mean±SD	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±SD	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.

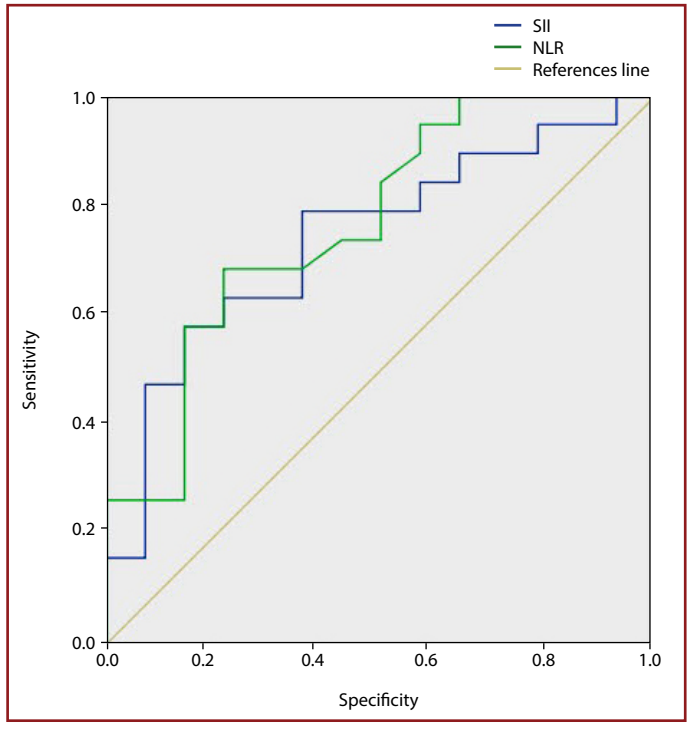

Figure 1. ROC curve analysis of lymphovascular invasion for NLR and SII.

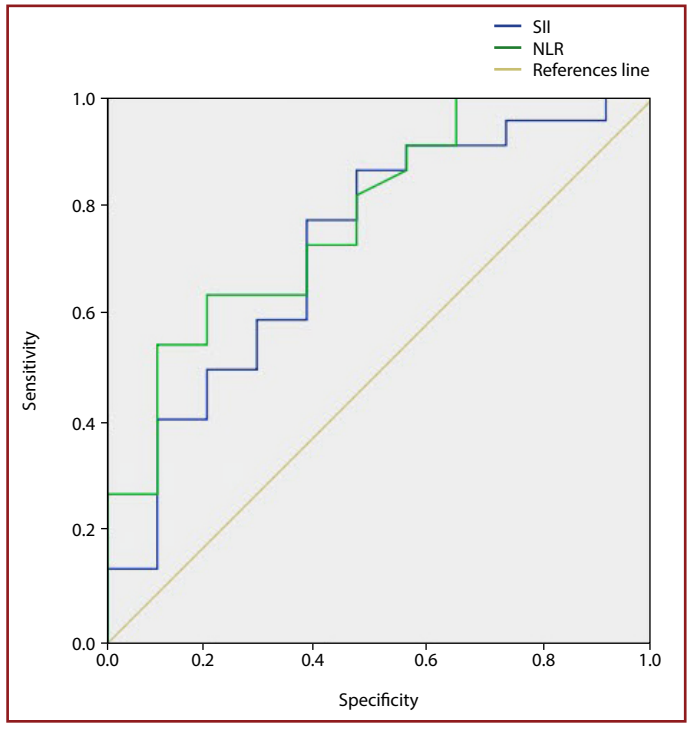

Figure 2. ROC curve analysis of perineural invasion for NLR and SII.

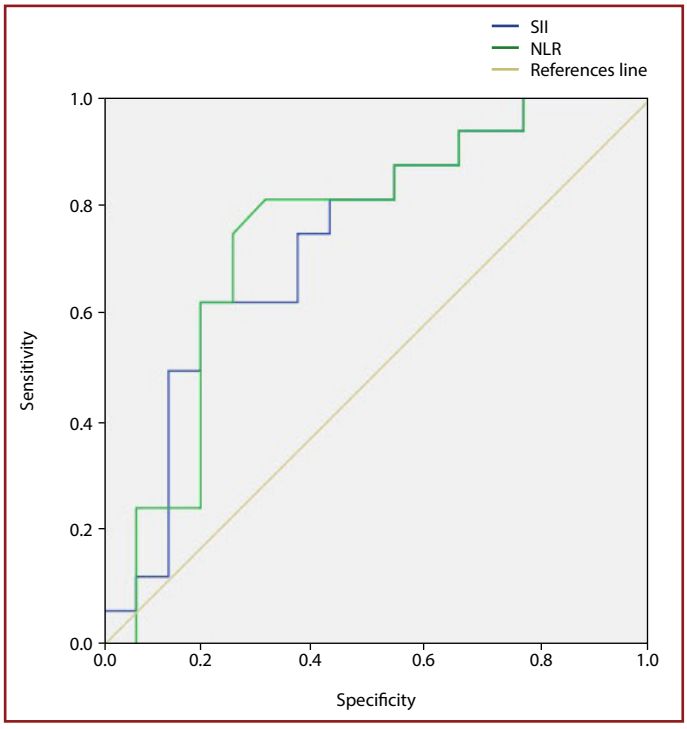

Figure 3. ROC curve analysis of extranodal extension for NLR and SII.

as 509.26. ROC curve analysis of lymphovascular invasion, perineural invasion, and extranodal extension for NLR and SII is demonstrated in Figures 1, 2, and 3 respectively.

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

The correlation of extranodal extension with NLR and SII in patients with tongue SCC is demonstrated in Table 4. Extranodal extension significantly correlated with NLR and SII (p=0.003, p=0.022, respectively).

The correlation of the pathological differentiation degree of tongue SCC with NLR and SII is in Table 5. There was no significant correlation between the pathological degree of tongue SCC and NLR and SII (p>0.05).

Discussion

The strong relationship between cancer and inflammation has been studied, and the effects of inflammatory cells in carcinogenesis have been widely reported. Tumor microenvironment, organized by inflammatory processes, leads to tumor angiogenesis, invasion, and metastasis [7]. Neutrophils cause tumor growth by producing proangiogenic factors, such as vascular endothelial growth factor, proteases, and chemokines, and enhance the adhesion of circulating tumor cells in distant sites [20. 21]. Platelets and the coagulation system also have an important role in cancer progression and facilitate the tumor cell adhesion to the endothelium and prevent cell death [22].

Lymphocytes inhibit the proliferation of tumor cells and restrain metastasis by cytokine production and induce 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]. Previous studies have shown that decreased L 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 PLR has

Table 4. 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's chi-Square test; *p<0.05.

Table 3. 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's chi-Square test; *p<0.05.

Table 5. Correlation of NLR and SII with the 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.

been revealed in several 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 weaker immune response in cancer patients. Elevated SII is associated with worse overall survival in several solid tumors [26]. Although the prognostic value of SII has been reported in different cancer types, the relationship between SII and tongue SCC has not been studied. Therefore, in this study, SII values were investigated in patients with tongue SCC, which demonstrated statistically higher values of SII in cancer patients than in 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. [13]. ROC analysis determined cut-off values for CRP levels, leucocytes, monocytes, lymphocytes, neutrophils, NLR, dNLR, LMR, and PLR, which showed significant differences between the oral SCC and control groups. Further, NLR was significantly directly associated with PLR, and LMR was significantly inversely associated with NLR and PLR.

Ong et al. [10] studied WBC count in patients with early tongue SCC and revealed that low pretreatment LMR and high PLR indicate poor survival in these patients. 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 showed that NLR, PLR, and SII were significantly correlated with local recurrence according to the cut-off values, whereas the usability of NLR, PLR, and SII in overall and disease-free survival were limited.

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

Conclusion

SII might be helpful to determine the clinical course of cancer patients. High pretreatment SII indicates possible increased perineural and/or lymphovascular invasion positivity and the presence of extranodal extension. Therefore, close follow-up is recommended for patients with high NLR and SII.

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Authorship Contributions: Concept: İ.D.; Design: İ.D.; Data Collection or Processing: İ.D., M.S.; Analysis or Interpretation: İ.D., M.S.; Literature Search: İ.D.; Writing: İ.D.

Conflict of Interest: None declared.

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