

Prognostic Significance of Inflammatory Markers in Patients with Oral Cavity Cancers

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Abstract

Introduction: In the present study, we aimed to evaluate the relationship between neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune inflammation index (SII) values and overall survival (OS) and disease-free survival (DFS) in patients undergoing radiotherapy (RT) with a diagnosis of oral cavity cancer (OCC).

Methods: 58 patients were included who were treated with a diagnosis of OCC who applied to Cumhuriyet University Faculty of Medicine Radiation Oncology Clinic between January 2009 and December 2018. Kaplan-Meier analysis was used to determine OS and DFS. Multivariate Cox regression analysis was also performed to detect independent prognostic factors.

Results: All patients had a squamous cell carcinoma (SCC) of the oral cavity composed of 50 tongue SCC and 8 buccal SCC. Cut-off values in ROC analysis: 954 [Area=0.665 (0.511-0.800), p=0.06] for SII, 174 [Area=0.659 (0.608-0.795), p<.001] for PLR and 3.2 [Area=0.699 (0.556-0.841), p=0.016] for NLR. Prognostic factors affecting OS were SII, PLR, NLR and age. SII, NLR, PLR and grade were statistically significant prognostic factors for DFS. However, SII was an independent prognostic factor.

Conclusion: In this study, high SII value was found to be an indicator of shorter OS and DFS in patients with OCC.

Keywords: Oral cancer, neutrophils, lymphocytes, platelets, inflammation.

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Introduction

Head and neck cancers are the 6th most common cancers worldwide. They constitute 6% of all cancers and 1-2% of cancer-related deaths.^[1] According to the cancer statistics data of ASCO (American Society of Clinical Oncology) in 2019, the number of newly diagnosed patients with oral cavity cancer (OCC) has been reported to be approximately 35,000.^[2] According to the cancer statistics data of the Ministry of Health-Turkey, between 2011-2015 13,778 cases with newly diagnosed head and neck cancers were recorded, and 25% of them were OCC.

Genetic susceptibility, viruses, autoimmunity, inflammatory mechanisms, hormonal and metabolic factors have been blamed for the pathogenesis of OCCs. Some proinflammatory cytokines have been measured to investigate the inflammatory mechanism of the oral cavity. The relationship between cancer and chronic inflammation first began with Rudolf Virchow's definition of leukocytes in tumor tissue.^[3,4] In studies on chronic inflammation having an effect on tumor development, metastasis, prognosis and treatment response, the relationship between systemic inflammation degree and cancer has been demonstrated using systemic inflammation markers including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune inflammation index (SII).^[5-11] In some studies, the increase in NLR has been associated with a negative prognosis in cancer patients.^[5-11] It has also been suggested that the survival of tumor cells and the development of metastasis are affected by the number of platelets.^[12-14] A prognostic indicator based on neutrophil, lymphocyte and platelet counts is expected to be more robust than an indicator based on only one factor. Therefore, in 2014, Hu et al^[15] developed an indication that they named the SII to predict the prognosis of patients after curative resection for hepatocellular carcinoma. According to the SII equation, preoperative peripheral blood platelets (P), and neutrophil (N) and lymphocyte (L) counts per liter were calculated. The researchers thus tested the hypothesis that a high SII score ($SII > 330 \times 10^9$ cells/L) negatively affected the differentiation and prognosis in these patients. However, some studies have investigated whether this SII threshold is appropriate for predicting prognosis in all cancer patients. Studies suggest that SII is a useful and accurate independent prognostic indicator for all types of tumor patients.^[16-19] Also, unlike many inflammatory cytokines, measurement of PLR, NLR and SII is thought to be a very practical and easily accessible method to detect inflamma-

tion without extra cost, as it can be easily calculated from a simple whole blood cell count (CBC).

In this study, we aimed to evaluate the relationship between NLR, PLR and SII values at the beginning of treatment and overall survival (OS) and disease-free survival (DFS) in patients undergoing radiotherapy (RT) with a diagnosis of OCC.

Materials and Methods

The study protocol was approved by the institutional review board (2020-03/10). Fifty-eight patients who were admitted to Cumhuriyet University Medical Faculty Radiation Oncology Clinic between January 2009 and December 2018 were treated with a diagnosis of OCC. Patient files were evaluated in terms of age, gender, method of treatment, perineural invasion, lymphovascular invasion, pathological grade, extracapsular invasion, smoking habit, tumor stage, comorbidity, recurrence and metastasis NLR, PLR and SII (Platelet x Neutrophil/Lymphocyte) values were calculated from the hemogram examination at the beginning of treatment.

All patients had a squamous cell carcinoma (SCC) of the oral cavity. Surgery was performed on 35 patients (60%). RT was applied to all patients after surgery. Also, 28 (48%) of the patients were added simultaneously to chemotherapy, in addition to RT. Conventional fractionated RT (60-70 Gy, from 1.8-2 Gy daily) was applied to 44 (76%) patients, whereas simultaneous integrated boost RT (54 Gy from 1.8 Gy longitudinal, 66-70 Gy from 2.33 Gy) was performed to 14 (24%) patients. All patients receiving concurrent chemoradiotherapy were given weekly cisplatin (35 mg/m²) simultaneously.

SPSS Version 23 was used for statistics. Descriptive tests (median, mean, standard deviation, etc.) for demographic data of the patients, Chi-square test to identify characteristics of the groups and Kaplan-Meier analysis to determine OS and DFS were used. Multivariate Cox regression analysis was also performed to detect independent prognostic factors. ROC analysis was performed to determine NLR, PLR and SII cut-off values. In ROC analysis, cut-off values were as follows; 954 [Area=0.665 (0.511-0.800), p=0.045] for SII, 174 [Area=0.659 (0.608-0.795), p<.001] for PLR and 3.2 [Area=0.699 (0.556-0.841), p=0.016] for NLR.

Results

Fifty patients had tongue SCC, whereas a buccal SCC

was presented in 8 patients. 67 (range, 23-90), 69% were male and 31% were female. According to their stages, 7 (12%) patients were in Stage I, 16 (28%) patients were in Stage II, 11 (19%) patients were in Stage III, 24 (41%) patients were in Stage IV and distant metastasis was absent in all patients. The patients' data regarding the pathological grades were present in 47 patients composed of 21 patients with grade 1, 17 patients with grade 2 and 9 patients with grade 3. Perineural invasion was present in 20 patients, whereas it was absent in 11 patients. Twenty-seven patients had no

records regarding perineural invasion. Extracapsular invasion was detected in 11 patients, but absent in 24 patients. The data of extracapsular invasion could not be obtained in 23 patients. Lymphovascular invasion was found in 9 patients.

Prognostic factors affecting OS were SII, PLR, NLR and age (<65 vs. ≥65 years). In multivariate analysis, high SII was found to be associated with increased extracapsular invasion and older age. The results of the analysis of prognostic factors affecting OS are detailed in Table 1. SII, NLR, PLR and grade were statistically significant prognostic factors for DFS, however, SII has been identified as an independent prognostic factor. Analysis results affecting DFS are shown in Table 2.

There was no relationship between SII and PLR and perineural invasion, lymphovascular invasion, grade, extracapsular invasion, smoking, age, stage, comorbidity, recurrence or metastasis (p>0.05). For NLR, a statistically significant difference was detected for disease stage (p=0.046). The disease stage of patients with

Table 1. Prognostic factors affecting overall survival.

| Univariate analysis | 5-year OS % | Median OS (month) | p value |
|------------------------------|-------------|-------------------|----------------|
| SII | | | |
| <954 | 47 | 59 | <0.001 |
| ≥954 | 8 | 17 | |
| PLR | | | |
| <174 | 54 | 54 | 0.019 |
| ≥174 | 17 | 17 | |
| NLR | | | |
| <3.2 | 48 | 59 | 0.001 |
| ≥3.2 | 11 | 18 | |
| Age | | | |
| <65 years | 48 | 42 | 0.039 |
| ≥65 years | 14 | 23 | |
| ECE | | | |
| No | 40 | 54 | 0.104 |
| Yes | 22 | 18 | |
| Stage | | | |
| Stage I | 42 | 54 | 0.211 |
| Stage II | 31 | 26 | |
| Stage III | 37 | 20 | |
| Stage IV* | 19 | 13 | |
| Multivariate analysis | HR | 95% CI | p value |
| SII | | | |
| <954 | 1 | 2.14-15.47 | 0.001 |
| ≥954 | 5.76 | | |
| Age | | | |
| <65 years | 1 | 1.32-10.04 | 0.012 |
| ≥65 years | 3.64 | | |
| ECE | | | |
| No | 1 | 1.14-7.58 | 0.025 |
| Yes | 2.95 | | |

HR: hazard ratio, OS: overall survival

* Stage IV disease without distant metastasis

Table 2. Prognostic factors affecting disease-free survival.

| Univariate analysis | 5-year DFS % | Median DFS (month) | p value |
|------------------------------|--------------|--------------------|----------------|
| SII | | | |
| <954 | 35 | 53 | <0.001 |
| ≥954 | 4 | 10 | |
| PLR | | | |
| <174 | 29 | 25 | 0.008 |
| ≥174 | 13 | 11 | |
| NLR | | | |
| <3.2 | 35 | 32 | <0.001 |
| ≥3.2 | 9 | 17 | |
| Grade | | | |
| Grade 1 | 11 | 13 | 0.036 |
| Grade 2 | 40 | 53 | |
| Grade 3 | - | 13 | |
| Stage | | | |
| Stage I | 29 | 32 | 0.201 |
| Stage II | 25 | 19 | |
| Stage III | 21 | 20 | |
| Stage IV* | 20 | 10 | |
| Multivariate analysis | HR | 95% CI | p value |
| SII | | | |
| <954 | 1 | 1.27-16.56 | 0.019 |
| ≥954 | 4.60 | | |

CI: Confidence Interval, DFS: disease-free survival, HR: hazard ratio

NLR<3.2 was determined as 4 (15%) patients stage I, 10 (37%) patients stage II, 7 (26%) patients stage III, and 6 (22%) patients stage IV. For patients with NLR≥3.2, the disease stage was found to be stage I in 3 (10%) patients, stage II in 6 (19%) patients, stage III in 4 (13%) patients, and stage IV in 18 (58%) patients. However, there was no relationship between NLR and perineural invasion, lymphovascular invasion, grade, extracapsular invasion, smoking, age, comorbidity, recurrence or metastasis. The OS curve is given according to SII in Figure 1, by age in Figure 2, and by extracapsular invasion in Figure 3. Figure 4 shows the DFS curve according to SII.

Discussion

Cancer cells live and grow with the chronic inflammation they create in their microenvironment. Although inflammation is thought to have a beneficial effect on the destruction of pathological cells, the inflammatory response, which is not organized and managed by cancer cells, leads to tumor development and tumor cell ability to escape the destructive effects of the immune system. Indeed, research in head and neck cancers has made it clear that the local, regional and systemic inflammatory response is dysfunctional.^[20,21] Neutrophils and platelets secrete inflammatory factors that inhibit apoptosis in tumor cells and directly contribute to the proliferation and metastasis of tumor cells.^[4,22-25] Lymphopenia occurring in tumor tissue also causes the immune response to be interrupted by the host.^[26]

Systemically increasing neutrophil-platelet count and decreasing lymphocyte count will lead to higher NLR, PLR and SII. Rachidi et al^[27] reported that neutrophils, lymphocytes and NLR have prognostic significance in these cancers in large cohort studies including all head and neck cancers (oral cavity, pharyngeal and laryngeal cancers). Ozturk et al^[28] demonstrated that NLR and PLR values are valuable markers in predicting local recurrence of tongue squamous cell cancers. Deveci et al^[29] reported that high SII values were associated with increased perineural/lymphovascular invasion and extranodal involvement. Chen et al^[30] reported that PLR was superior to NLR in predicting DFS and OS in oral squamous cell cancers. Ma et al^[31] identified a cut-off value of 4.0 for NLR and reported that NLR was an independent prognostic factor for primary lymphoepithelioma-like carcinomas of salivary glands. In our study, the cut-off value for NLR was found to be 3.2

and median, 5-year and DFS were found to be better in those with NLR<3.2.

High SII, NLR and PLR values were shown to be significantly associated with negative survival in hepatocellular carcinoma, esophageal squamous cell carcinoma, pancreatic cancer, melanoma and small cell lung cancer.^[16,32-34] In addition to SII, other inflammatory and immune-related parameters such as NLR and PLR have been reported to have prognostic significance among various cancers.^[35,36] High preoperative NLR and PLR values were associated with an increased risk of death and poorer survival in OCCs.^[30]

Our study revealed that particularly high SII is associated with decreased OS and DFS in OCCs. NLR and PLR values also affected OS and DFS, but only SII elevation has been determined as an independent prognostic factor. 5-year and median OS survival in patients with SII<954 was 47% and 59 months, respectively, and 8% and 17 months for patients with SII≥954. In patients with SII<954, 5-year and median DFS was 35% and 53 months, respectively and 4% and 10 months for patients with SII≥954. In multivariate analysis, the hazard ratio was 5.76 for OS whereas it was 4.6 for DFS. In SII, NLR and PLR calculations, it should be taken into consideration that the elevation of these values may be due to neutrophil and platelet elevation and/or lymphocyte depletion. For this reason, a CBC should be examined in detail before treatment.

Previous data have shown that SII, NLR and PLR are significantly associated with the aggressive properties of cancer.^[16,33] Larger tumor size, poor differentiation, tumor recurrence or metastasis have been found to be more likely in patients with high SII.^[33-37] However, in our study, NLR, PLR and SII elevation did not correlate with grade, perineural invasion, lymphovascular invasion, recurrence or metastasis, while OS and DFS were correlated with SII, NLR and PLR. The disease stage was also found to be more advanced in patients with elevated NLR.

Conclusions

High SII value may be an indicator of shorter OS and DFS in patients with OCC. Due to its reproducible, easy to calculate and low-cost features, SII can be considered as a promising parameter to evaluate the prognosis of OCC. A larger and appropriately designed prospective study is necessary to confirm the prognostic value of SII in OCC before being used in daily clinical practice.

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Ethics Committee Approval: The study protocol was approved by the institutional review board (2020-03/10).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Author Contributions: Designing the study – E.E.; Collecting the data – B.Y.; Analysing the data – B.Y.; Writing the manuscript –E.E.; Confirming the accuracy of the data and the analyses – E.E., B.Y.

Conflict of Interest: The authors have no conflicts of in-terest to declare.

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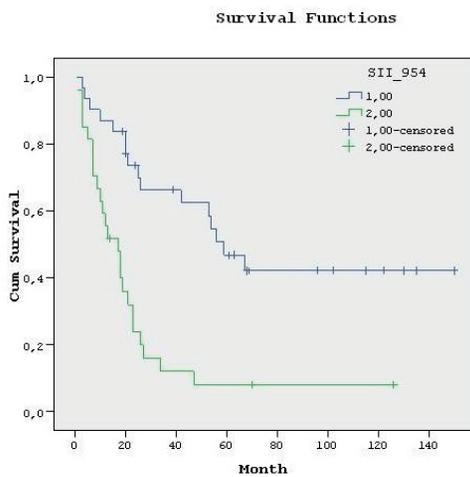


Figure 1. Overall survival curve according to SII.

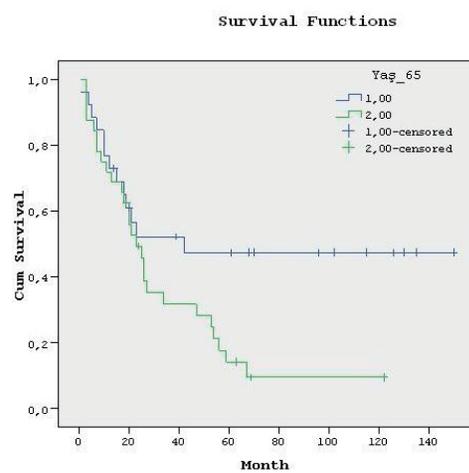


Figure 2. Overall survival curve by age.

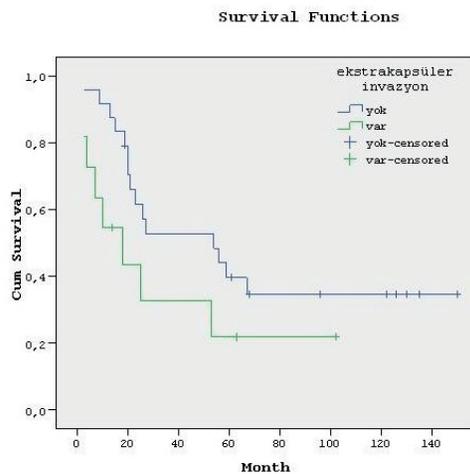


Figure 3. Overall survival curve according to extracapsular invasion.

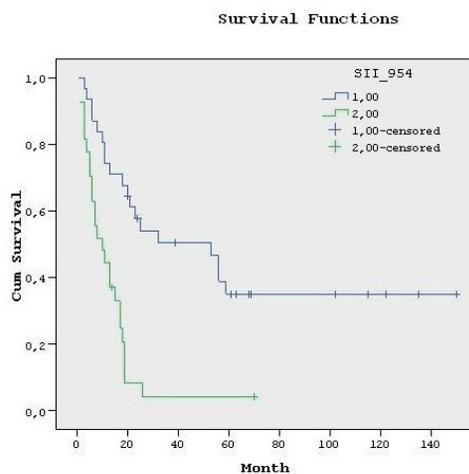


Figure 4. Disease-free survival curve according to SII.

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