Prognostic value of baseline and posttreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in head and neck squamous cell carcinoma receiving chemoradiotherapy

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Abstract

Objective: The aim of this study was to evaluate the prognostic value of baseline and posttreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in head and neck squamous cell carcinoma (HNSCC) receiving chemoradiotherapy (CRT).

Material and methods: Ninety-two HNSCC patients who received adjuvant or primary radiotherapy (RT) between September 2014 and December 2019 were assessed retrospectively. Surgery was performed on 24 (26.1%) patients. Eight patients (8.7%) received induction chemotherapy (CT), 63 patients (68.5%) concomitant CT and 17 (19.5%) patients received adjuvant CT.

Results: The median follow-up time was 19 months (range 1-61 months). The median overall survival (OS) and progression-free survival (PFS) were 16 and 13 months, respectively. High baseline NLR level was found to be significantly associated with advanced T stage. Survival was significantly poor if baseline NLR cut-off was above 2.7. No significant correlation was revealed between post-RT NLR, baseline PLR and post-RT PLR and OS. Advanced T stage, presence of metastasis and high post-RT PLR were found to be significant factors that decrease PFS.

Conclusion: High baseline NLR level in HNSCC receiving CRT/RT was strongly associated with advanced T stage and poor prognosis. However, well designed, larger studies with longer follow-up are warranted.

Keywords: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), head and neck cancer, chemoradiotherapy, prognosis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world (1). In its treatment, the cure is provided by surgery and /or adjuvant radiotherapy (RT) or primary chemoradiotherapy (CRT) (2,3). Despite this, 5-year survival rates are around 50% (4,5). Local recurrence and distant metastasis are the main causes of failure. TNM staging has been established with a certain role in determining the prognosis of the disease. The anatomic spread of tumor predicts prognosis (3-5).

Many factors such as genetic, viral infection status (HPV), hormonal and metabolic factors, autoimmunity and inflammation are blamed in the pathogenesis of head and neck cancers (HNC) (2,3). Inflammation plays an important role in tumorigenesis and tumor progression (6, 7).

The relationship between cancer and inflammation was first expressed by the German pathologist Rudolf Virchow in 1863 and has been more widely investigated for the last two decades (8, 9).

Many laboratory tests associated with the systemic inflammatory process, such as C-reactive protein, albumin, hemoglobin, white blood cell components have been investigated as prognostic and predictive markers in various cancer types. Peripheral inflammatory cells and their ratio, especially neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been demonstrated to be independent prognostic factors in some types of solid cancer (10-13). In recent years, many studies have suggested that high NLR, an increase in neutrophil level and/or a decrease in lymphocyte level, indicate a poor prognosis in HNCs (14-16).

Based on the prediction that higher NLR and PLR are related to worse disease and poor survival, we retrospectively examined our series of HNC treated with CRT in our department. In this study, it was aimed to evaluate the independent predictor effect of NLR and PLR in patients with HNSCC receiving RT.

Material and methods

Patients Selection

Ninety-two HNSCC patients who received adjuvant or primary radiotherapy at Tokat Gaziosmanpasa University University Radiation Oncology Clinic between September 2014 and December 2019 were evaluated retrospectively. Patient interview information, patient files and electronic system data were used for the study. The demographic status, primary diagnoses, standard hemogram values, stage of the disease, treatment type, response to therapy and final status of the patients were noted.

Patients who had no bone marrow problem for any reason had normal biochemistry values and had complete file information and follow-up's were included in the study. Patients with secondary malignancy in the last five years, who have previously received RT in the head and neck region, and those under 18 years were excluded. In addition that, the patients with the use of drugs that have a direct effect on white blood cell (WBC), such as steroids, or infected patients were excluded from the study. Hemogram values within 7 days before RT were noted for baseline NLR.

Treatment Details

All patients were evaluated at the multidisciplinary treatment council before treatment. Patients were staged according to AJCC TNM staging classification (8th edition). With the Varian Clinac DHX Linac device, RT was delivered to the patients a total dose range 60-70 Gy in 30-35 fraction with IMRT technique. Cisplatin (40 mg/m2) weekly was administered to 68.5% of the patients simultaneously with RT. Patients were invited to the 3-month controls after treatment and their tests were performed.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)

According to the results of peripheral blood evaluation, NLR was calculated as absolute neutrophil/absolute lymphocyte count and PLR was calculated as absolute thrombocyte count/absolute lymphocyte count. ROC curve analysis was used for the cut-off value.

The primary endpoints

The primary endpoint of the study was whether NLR and PLR affect overall survival (OS) and progression-free survival (PFS). The endpoint for the OS was the exitus date for the dead patients and the last control date for the surviving patients. The endpoint for PFS was the progression date for patients progressing, the last control date for surviving patients, and the exitus date for the deceased.

The study was conducted in accordance with Helsinki declaration and this was approved by the Institutional Ethics Committee of Gaziosmanpaşa University.

Statistical Analysis

For the statistical analysis, SPSS 24 (IBM Corp., Armonk, NY) was used. The categorical demographic characteristics of the patients were calculated with Chi-square and Fisher's exact test. In the survey analysis, Kaplan Meier was utilized and compared with the log-rank test. Also, Cox proportional hazards model was employed in multivariate analyzes. A $p \leq 0.05$ was considered as statistically significant. The receiver operating characteristic (ROC) curve (AUC) test was used for the predictive value of PLR, NLR and other hematological parameters. Hazard ratio (HR) and 95% confidence interval (CI) values of statistically significant parameters were noted. If HR> 1, it is accepted that there is an increased relative risk according to the reference category.

Results

Patient characteristics

The median follow-up period of 92 patients with HNSCC who received RT was 19 months (range 1-61 months). The median age was 62 years (range, 25-88 years) and 75 (81.5%) patients were male. Surgery was performed on 24 (26.1%) patients. Eight patients (8.7%) received induction chemotherapy (CT), 63 patients (68.5%) concomitant CT and 17 (19.5%) patients received adjuvant CT. The patients with clinical T3 (cT3) tumors were the most frequently observed with 33 patients (35.9%); There were 43 (46.7%) patients with lymph-node negative and only 2 (2.2%) patients with metastatic disease. The patient and characteristics are shown in Table 1 in detail.

While 67 patients (72.8%) were alive during the follow-up period, 25 (27.2%) died. Local recurrence was observed in 11 (12%), distant metastasis in 5 (5.4%) and local recurrence + distant metastasis in 3 (3.3%) patients. The median OS was 16 months (1-61 months). The 1-year, 2-year and 3-year OS rates were 81.6%, 73.4% and 65.3%, respectively. The median PFS was 13 months (range 1-61 months). The 1-year, 2-year and 3-year PFS rates were 72.8%, 66% and 52.2%, respectively.

Overall survival and NLR/PLR relation

The relationship between OS and the variables was evaluated by COX regression analysis (Table 2). The relationship between OS and cT stage and baseline NLR was found to be significant. The median OS for cT1-2 patients was 24 months (range, 3-61 months), while for patients with cT3-4 was 11 months (range, 1-57 months) (p0.005) (Figure 1).

The median OS was 17 months (range,1-61 months) in the patients with baseline NLR cut off value ≤2.7, whereas the median OS was 13 months (range,1-58 months) in the patients with baseline NLR cut off value >2.7 (p0.046) (Figure 1).

As a result of ROC curve analysis, a significant correlation was detected between baseline NLR and OS. For the threshold value NLR 2.7, sensitivity was 66.7% and specificity was 42.6%. (p0.024; AUC 0.65; 95% Confidence Interval: 0.534-0.782) (Figure 2). As a result of the ROC curve analysis for post-RT NLR, baseline PLR and post-RT PLR, no significant correlation was observed between all these variables and OS (Table 3).

Progression-free survival (PFS) and NLR/PLR relation

The relationship between PFS and the variables was evaluated by COX regression analysis. PFS was found to be significantly associated with cT stage, metastasis status and post-RT PLR (Table 4).

The median PFS was 17 months (range, 2-61 months) in the patients with cT1-2, while 5 months (range, 1-53 months) in the patients with cT3-4 (p0.007) (Figure 3).

The PFS was 2 and 8 months in two patients who had metastasis and the median PFS was 16 months (range, 1-61 months) in the remaining patients without metastasis (p0.021) (Figure 3). The median PFS was 18 months (range, 1-58 months) in the patients with post-RT PLR ≤ 326, whereas 5 months (range, 1-61 months) in the patients with post-RT PLR >326 (p 0.050) (Figure 3).

As a result of ROC curve analysis for PFS, there was no significant correlation between baseline NLR, post-RT NLR, baseline PLR, post-RT PLR and PFS (Table 5). In ROC curve analysis, there was no significant result between post-RT PLR and PFS. However, when cox analysis was performed, the result was close to the limit of significance (p0.42; AUC 0.55; 95%Confidence Interval: 0.424-0.682) (Figure 4). In order to clarify this situation, longer follow-up required and more patients should be included in the study.

Table 1. Patient characteristics

Age	Median (range)	62 (aralık 25-88)
	65> N (%)	56 (60.9%)
	65≤ N (%)	36(39.1%)
Gender, N (%)	Female	17(18.5%)
	Male	75(81.5%)
Oncological Surgery	No	68(73.9%)
	Yes	24(26.1%)
Induction CT	No	84(91.3%)
	Yes	8(8.7%)
Concurrent CT	No	29(31.5%)
	Yes	63(68.5%)
Adjuvant CT	No	17 (19.5%)
	Yes	75 (81.5%)
Site of primary tumor, N (%)	Nasopharynx	22(24.4%)
	Hypopharynx	1(1.1%)
	Larynx-Glottis	23(25.6%)
	Larynx-SupraGlottis	22(24.4%)
	Larynx-SubGlottis	4 (4.4%)
	OralCavity	14(15.2%)
	Unknown Primary	1(1.1%)
cT Stage	cT1	23(25%)
	cT2	18(19.6%)
	cT3	33(35.9%)
	cT4	18(19.6%)
cN Stage	cN0	43 (46.7%)
	cN1	8(8.7%)
	cN2	33(35.9%)
	cN3	2(2.2%)
	Missing	6(6.5%)
Metastasis	No	90(97.8%)
	Yes	2(2.2%)
NLR	Baseline	2.73(1.05-18.0)
	Post-RT	5.2(1.6-13.75)
PLR	Baseline	134(25-430)
	Post-RT	326(35-771)

Table 2. Cox regression analysis of OS

		HR (95% CI)	p
Age	65<, N (%)	1.71(0.77-3.97)	0.18
Gender	Male vs female	1.62(0.63-4.14)	0.30
Operation	Opereted vs non-opereted	0.20(0.013-3.37)	0.26
Clinic T Stage	cT1-2 vs cT3-4	3.80(1.49-9.72)	0.005*
Clinic N Stage	cN0 vs cN1-3	0.78(0.34-1.79)	0.57
Metastasis	Yes vs no	0.047(0.041-0.87)	0.58
Baseline NLR	2.7 lower vs higher	2.38(1.09-5.79)	0.046*
Post-RT NLR	5.2 lower vs higher	1.06(0.29-3.82)	0.92
Baseline PLR	134 lower vs higher	1.25(0.52-2.97)	0.60
Post-RT PLR	326 lower vs higher	1.97(0.84-4.63)	0.11

CI confidence interval, HR hazard ratio, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 3. ROC analysis of PLR and NLR for overall survival

	Cut off	AUC	95% CI	p
Baseline NLR	2.7	0.65	0.534-0.782	0.024*
Post-RT NLR	5.2	0.61	0.487-0.745	0.16
Baseline PLR	134	0.52	0.394-0.657	0.71
Post-RT PLR	326	0.59	0.469-0.726	0.17

CI confidence interval, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 4. Cox regression analysis of PFS

		HR (95% CI)	
Age	65<, N (%)	1.95(0.97-3.91)	0.059
Gender	Male vs female	1.54(0.69-3.54)	0.29
Operation	Opereted vs non-opereted	0.20(0.145-1.65)	0.96
Clinic T Stage	cT1-2 vs cT3-4	2.72(1.30-5.69)	0.007*
Clinic N Stage	cN0 vs cN1-3	0.83(0.41-1.69)	0.62
Metastasis	Yes vs no	5.58(1.291-24.144)	0.021*
Baseline NLR	2.7 lower vs higher	1.56(0.771-3.168)	0.21
Post-RT NLR	5.2 lower vs higher	1.62(0.79-3.34)	0.18
Baseline PLR	134 lower vs higher	1.37(0.68-2.76)	0.36
Post-RT PLR	326 lower vs higher	2.02(1.03-4.09)	0.050*

CI confidence interval, HR hazard ratio, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 5. ROC analysis of PLR and NLR for progression-free survival

	Cutt off	AUC	95%Confidence Interval	p
Baseline NLR	2.7	0.60	0.480-0.728	0.10
Post-RT NLR	5.2	0.57	0.443-0.701	0.28
Baseline PLR	134	0.46	0.342-0.589	0.59
Post-RT PLR	326	0.55	0.424-0.682	0.42

CI confidence interval, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

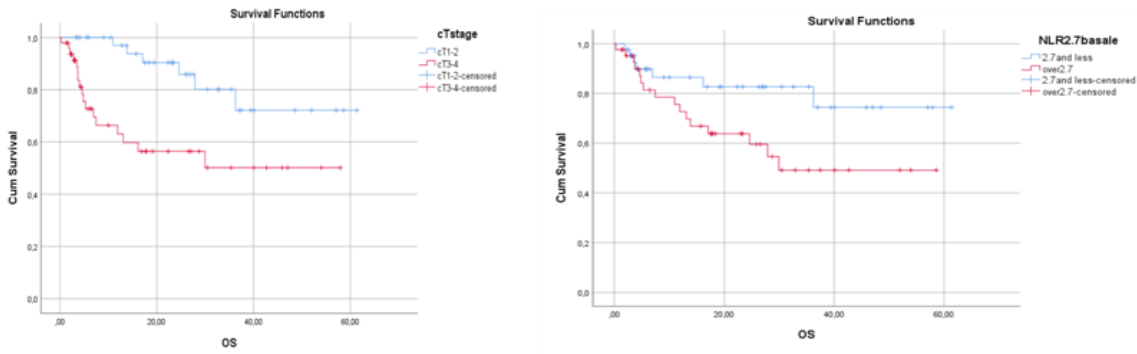**Figure 1.** The relation between OS and baseline NLR/ cT stage

Figure 2. The relation between OS and baseline NLR in ROC analysis
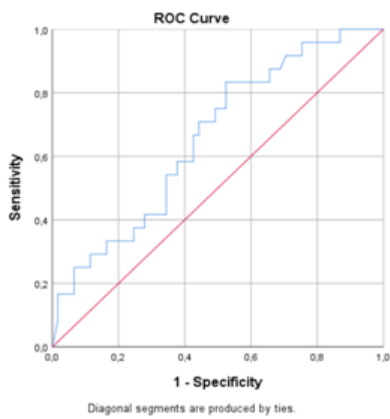

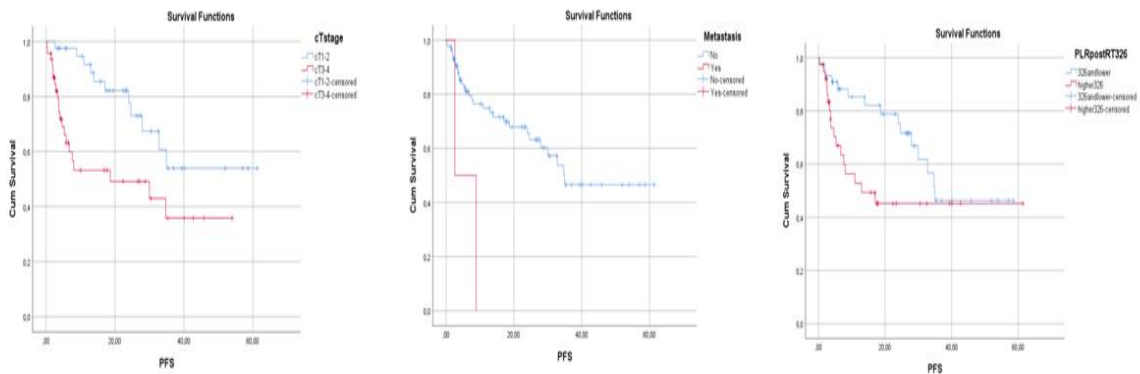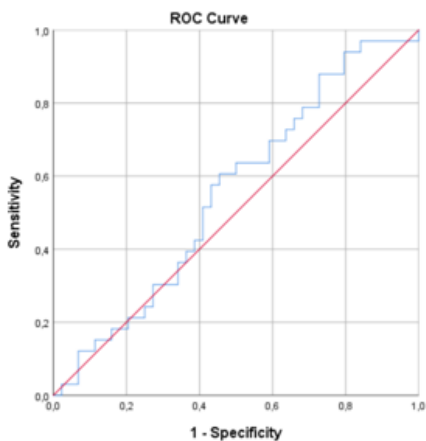**Figure 3.** The relation between PFS and cT stage/ metastasis status/post-RT PLR

Figure 4. The relation between PFS and post-RT PLR in ROC analysis

Discussion

The tumor microenvironment has an important role in tumor proliferation, invasion and metastasis. The two main factors associated with tumor microenvironment are tumor oxygenation and antitumoral immunity, which increase the sensitivity of the tumor to radiation. Immunity, inflammation and cancer are intertwined concepts (17,18). Based on this, many inflammatory markers have been investigated in terms of being prognostic and predictive recently. In particular, hematological parameters are valuable not only because they can be easily done in almost all centers, but also because they give an idea of tumor oxygenation and systemic inflammation. In the present study, we retrospectively analyzed the hematological markers of 92 patients with HNSCC before and after the RT or CRT. As a result of our study, high baseline NLR level was found to be significantly associated with advanced T stage. Survival was significantly poor if baseline NLR cut-off was above 2.7. No significant correlation was revealed between post-RT NLR, baseline PLR and post-RT PLR and OS. Advanced T stage, presence of metastasis and high post-RT PLR were found to be significant factors that decrease PFS. The median PFS was 18 and 5 months below and above post-RT PLR 326, respectively. According to the ROC curve analysis of our study, baseline NLR/PLR and post-RT NLR/PLR levels were not prognostic for PFS, whereas solely baseline NLR was displayed to be a significant prognostic marker for OS.

In the study of Haddad et al. they evaluated 46 advanced stage HNC patients treated with CRT, a significantly better 2-year OS was reported if NLR <5 (16). In the study on oral cavity tumors with 400 patients in which median follow-up time was 36 months, Malik et al found that NLR and PLR values are predictive for treatment results and survival (NLR cut off 2.5, PLR cut off 100) (19). In another study conducted with 153 patients with p16-negative squamous cell carcinoma of unknown primary in Head and Neck, the pre-operative NLR >6 was associated with poor prognosis (20). In the study of Lai et al, 126 local advanced HNC patients receiving induction CT was evaluated and NLR was reported to be prognostic for evaluating the response to induction CT (21). In their meta-analysis Yang et al. evaluated 6847 patients in 2019, NLR was reported to have a significant prognostic value for disease-free survival (DFS), cancer-specific survival (CSS) and PFS, but no significant effect for PLR (22). Similarly, in our retrospective series of 92 patients, we also demonstrated that baseline NLR was a prognostic marker, but PLR was not prognostic.

In the other study with 167 p16-positive oropharyngeal squamous-cell carcinoma patients treated with CRT, both NLR and anemia have been shown as prognostic (23). Significantly higher disease recurrence was observed in patients with NLR> 5 (23). In a retrospective study including 120 patients with hypopharyngeal cancer who received definitive CRT, the prognostic role of pretreatment serum NLR was investigated. The NLR has been shown as both independent prognostic and predictive of the CRT response, with a cut off 4. The high pretreatment NLR level was correlated with poor treatment response and reported to be prognostic for PFS (24). In the present study, the prognostic significance of both pretreatment and posttreatment NLR/PLR were examined. Similar to the many studies mentioned above, only pretreatment NLR (cut off 2.7) was found prognostic for OS. However, any correlation between OS and posttreatment NLR could not be demonstrated. Contrary to, Kim et al (25) reported that posttreatment NLR elevation was also associated with poor prognosis in their study with 104 HNSCC patients treated with CRT (25).

The study examining the prognostic significance of PLR was conducted with 247 patients with nasopharyngeal cancer who received CRT (26). Similar to our study, when NLR and PLR were analyzed with curve analysis, NLR was shown to be independent prognostic for OS and PFS but PLR was not prognostic (26).

The limitations of the study were that it was retrospective and performed with a heterogeneous group at a single-center. Furthermore, if the follow-up time was long, analysis of whether PLR is a prognostic marker could have been significant results.

Conclusion

High baseline NLR level in HNSCC receiving CRT/RT was strongly associated with advanced T stage and poor prognosis. Significantly worse PFS was also found at high post-RT PLR level. However, well designed, larger studies with longer follow-up are warranted.

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