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The association of anemia and high neutrophil-lymphocyte ratio with decreased survival in patients with laryngeal cancer treated with radiotherapy

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ABSTRACT

Aims: We aimed to examine the prognostic value of inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and anemia on oncological outcomes in patients with laryngeal squamous cell carcinomas (LSCC) treated with radiotherapy.

Methods: 213 LSCC patients analyzed retrospectively. Inflammatory markers were established by examining blood samples taken within 7 days before treatment. Patients were categorized into two groups: low and high according to NLR, PLR, and SII threshold values. In addition, to evaluate the effect of hemoglobin (Hb) level, the threshold value of each inflammatory marker and Hb level were combined, and 3 groups were formed (3 groups for NLR, 3 groups for PLR, and 3 groups for SII). The relationship between inflammatory markers and overall survival (OS), disease-free survival (DFS), and local regional recurrence-free survival (LRRFS) was investigated.

Results: In univariate analysis, high NLR, PLR, SII, and low Hb (<13 g/dl) level were associated with worse survival (all p<0.022), except for PLR and Hb for LRRFS. OS and DFS were significantly better in patients in each group A with a low inflammatory index and high Hb (all p<0.013). In the multivariate analysis, high NLR and group CNLR (high NLR with low Hb) were statistically significant predictors of decreased OS (HR 1.85, 95% CI 1.05-3.28, p=0.033; HR 2.61, 95% CI 1.14-5.97, p=0.022) and DFS (HR 1.81, 95% CI 1.11-2.96, p=0.017; HR 3.32, 95% CI 1.20-9.16, p=0.028).

Conclusion: NLR may serve as a potential prognostic biomarker in LSCC, and its predictive ability is further enhanced when NLR is combined with Hb level.

Keywords: Anemia, laryngeal squamous cell carcinoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, radiotherapy, systemic immune-inflammation index

INTRODUCTION

Laryngeal squamous cell carcinomas (LSCC) are the most frequently seen cancers among head and neck cancers (HNC).[1] Currently, the two main treatment modalities used to treat LSCC in the absence of distant metastases are surgical excision and radiotherapy (RT).[2,3] It has been stated in systemic reviews that surgery and RT are similarly effective in the management of early-stage LSCC, and there is no difference in terms of local control rates.[4] Moreover, in early-stage LSCC, RT is preferred as it gives satisfactory results in terms of sound quality.[5] In addition, after prospective randomized studies showed that there is no difference in survival between chemoradiotherapy (CRT) and surgery in advanced-stage LSCC, this approach, which can provide larynx preservation, has become a standard treatment in selected advanced stages.[6,7] With definitive RT, it is possible to obtain better psychosocial and functional results by preserving voice and swallowing function instead of the worsened quality of life caused by surgery. Although it varies according to the stage of the tumor, the site of the disease, and the patient's preference, RT is a frequently preferred modality since it enables laryngeal preservation. Moreover,

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in the presence of adverse features, the necessity of adjuvant RT or adjuvant CRT in the postoperative setting is still valid.[8]

The response to RT may differ between patients; unfortunately, recurrence can be encountered over time. Host-related factors and tumor characteristics are factors that affect treatment response and survival. While age, gender, and performance status constitute the host-related factors, stage, lymphovascular invasion (LVI), perineural invasion (PNI), p53 mutations are some of the tumor-related factors.[9,10] While these are not entirely sufficient to predict survival, they can help to some extent determine the prognosis. Therefore, it is of great importance to search for reliable prognostic markers to predict survival.

Data from the literature suggest that anemia affects the prognosis of patients with HNC treated with RT.[11] The hemoglobin (Hb) level is an indicator of the oxygen-binding capacity of the blood. Low Hb levels are thought to be associated with hypoxia, resulting in resistance to RT, and thus with a poor prognosis.[11,12]

A growing body of evidence in recent years has demonstrated that systemic inflammation plays a crucial role in tumorigenesis and progression, so many researchers have extensively focused on investigating the relationship between cancer prognosis and inflammation-based parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), which reflects the balance of host inflammatory and immune status.[13-16]

To the best of our knowledge, these indices have been shown to predict oncological outcomes in various tumor types, but fewer are reported for LSCC.[12,14-16-20] These simple hematological parameters can be useful in determining the prognosis of LSCC in daily practice. We hypothesized whether the predictive effect could be enhanced by combining low Hb levels, which are an indicator of hypoxia, and high NLR, PLR, and SII values, which are thought to be associated with tumorigenesis and progression, thus we aimed to examine the prognostic value of inflammatory markers (NLR, PLR, SII) and anemia on overall survival (OS), disease-free survival (DFS) and local regional recurrence free survival (LRRFS) in LSCC patients treated with RT.

METHODS

Ethics

This study was approved by the institutional review board of our institute and was conducted in accordance with the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients. The study was initiated with the approval of the Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No: 10/11).

Study Population

LSCC patients referred to the Radiation Oncology Clinic of Samsun University Samsun Training and Research Hospital between January 2012 and December 2017 and who received RT were reviewed retrospectively. Patients older than 18 years old with a histopathological diagnosis of LSCC, treated with definitive RT/CRT or adjuvant RT/CRT were included. Patients who used steroid therapy or have had acute or chronic inflammatory diseases or hematological disorders and a second malignancy were excluded. Blood samples were taken within one week before RT start or oncologic surgery.

Clinical Data Collection

A retrospective chart review was performed. The data, including patient demographics, laboratory parameters, imaging reports, clinicopathological characteristics, treatment, and oncological outcomes were extracted through the patient archive files and electronic medical records system. Hb, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), uric acid, and albumin levels were recorded by examining the blood samples taken within 7 days before the treatment. NLR is defined as the absolute neutrophils count divided by lymphocyte count, and PLR is defined as the absolute platelet count divided by lymphocyte count. SII was defined according to this formula: platelet counts × neutrophil counts/lymphocyte counts. Anemia was defined as a Hb level of <13 g/dL.

After determining the optimal cut-off values for NLR, PLR, and SII, the patients were divided into two groups, low and high, according to these values. In addition, to evaluate the effect of Hb level (13 g/dL), the threshold values of each inflammatory marker and Hb level were combined, and three groups were formed. Patients were grouped as follows for NLR: Group ANLR, low NLR and high Hb, Group BNLR, low NLR and low Hb or high NLR and high Hb, Group CNLR, high NLR and low Hb. Patients were grouped as follows for PLR: Group APLR, low PLR and high Hb, Group BPLR, low PLR and low Hb or high PLR and high Hb, Group CPLR, high PLR and low Hb. Patients were grouped as follows for SII: Group ASII, low SII and high Hb; Group BSII, low SII and low Hb or high SII and high Hb; Group CSII, high SII and high Hb.

Treatment and Follow-up

Patients were treated with definitive RT/CRT or adjuvant RT/CRT. In early-stage tumors, usually the hypofractionated regimen (63 Gy in T1N0 tumors and 65.25 Gy in T2N0 tumors with 2.25 Gy fraction (fx) per day) was preferred; otherwise, they were treated with a conventional scheme of 66-70 Gy with 2 Gy fx per day. Patients were treated with the 3-dimensional conformal RT technique. On the other hand, advanced-stage LSCC patients were treated with the intensity-modulated RT technique. With a daily fraction of

2 Gy, a total of 70 Gy was given for definitive RT, while a total of 60-66 Gy was given as adjuvant. In some patients who underwent definitive treatment, 69.96 Gy (2.12 Gy/fx to 69.96 Gy; 1.8 Gy/fx to 59.4 Gy; 1.64 Gy/fx to 54.12 Gy) was administered in 33 fractions using the simultaneous integrated boost technique. Concomitant chemotherapy was administered with definitive RT in the advanced-stage and with adjuvant RT in the presence of risk factors. During RT, intravenous chemotherapy (35-40 mg/m² cisplatin) once a week or once every 21 days (75-100 mg/m² cisplatin) was administered.

Patients were followed up with laryngoscopic and physical examinations for 4-6 weeks after RT, and every 3 months during the first 2 years, every 6 months for the next 3 years, and annually thereafter. Radiological imaging, including computed tomography and/or positron emission tomography, was performed at the initial follow-up to assess treatment response and in subsequent follow-ups in the presence of clinical suspicion based on physical examination and/or laryngoscopy findings. Based on clinical, radiological, and/or histological findings, loco-regional recurrence was defined as primary tumor regrowth or cervical lymph node involvement; detection of any metastasis in solid organs was accepted as distant metastasis.

Statistical Analysis

The endpoints of the study were OS, DFS, and LRRFS. OS was defined as the interval between the date of diagnosis and death from any cause until the last follow-up. DFS was defined as the interval between the date of diagnosis and the date of occurrence of local, regional, or/and distant failure, whichever comes first, or death until the last follow-up. LRRFS was defined as the interval between the date of diagnosis and the detection of loco-regional recurrence or death from any cause until the last follow-up. Patients were followed up regularly from the date of diagnosis to May 2018, or the date of death.

Continuous variables are presented as the medians, and categorical variables are presented in order of frequency. Receiver Operating Characteristics (ROC) curve analysis was used to determine the optimal cut-off point for NLR, PLR, and SII for prediction of survival. Chi-squared and Fisher's exact tests were used for comparisons between NLR, PLR, SII, and clinicopathological characteristics. The Kaplan-Meier method and log-rank test were utilized to analyze and compare the survival rates. Cox proportional hazards models were used for univariate and multivariate analyses. The hazard ratios (HR) with 95% confidence intervals (CI) and p values were reported. All statistical analyses were performed using SPSS 25.0 statistical software (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant. Bonferroni correction was used to adjust p-value for parameters categorized into 3 groups (p<0.017).

RESULTS

Patient Characteristics

Clinicopathological characteristics of the 213 LSCC patients included in our study, 159 of whom received definitive RT and 54 received adjuvant RT, are shown in **Table 1**.

Table 1 Clinicopathological characteristics

Variable	N (%)
Age (median)	61 (26-87)
Gender	
Female	4 (1.9)
Male	209 (98.1)
Localization	
Glottic	148 (69.5)
Supraglottic	63 (29.6)
Subglottic	2 (0.9)
Anterior commissura invasion	
-	62
+	56
Unknown	95
Subglottic extension	
-	93
+	25
Unknown	95
T stage	
T1	91 (42.7)
T2	34 (18.3)
T3	36 (16.9)
T4	47 (22.1)
N stage	
N0	164 (77)
N1	20 (9.4)
N2	24 (11.3)
N3	5 (2.3)
Stage	
1	91 (42.7)
2	31 (14.6)
3	31 (14.6)
4	60 (28.7)
Surgery	
-	159 (74.6)
+	54 (25.4)
Lymphovascular invasion	
-	18 (33.3)
+	36 (66.7)
Perineural invasion	
-	43 (79.6)
+	11 (20.4)
Extracapsular extension	
-	48 (88.9)
+	6 (11.1)
Treatment	
Definitive RT	121 (56.8)
Definitive CRT	38 (17.8)
Adjuvant RT	24 (11.2)
Adjuvant CRT	30 (14.2)
RT Schedule/Dose	
Hypofraction	
Stage 1 (63 Gy)	52 (24.5)
Stage 2 (65.25 Gy)	10 (4.7)
Conventional, definitive	
Stage 1 (66-70 Gy)	39 (18.3)
Stage 2 (68-70 Gy)	20 (9.3)
Stage 3 (70 Gy)	17 (8)
Stage 4 (70 Gy)	21 (9.9)
Conventional, adjuvant	
Stage 2 (66 Gy)	1 (0.4)
Stage 3 (60-66 Gy)	14 (6.6)
Stage 4 (60-70 Gy)	39 (18.3)
RT Technique	
Conformal	121 (56.8)
IMRT	86 (40.4)
SIB	6 (2.8)
Chemotherapy schema	
Once a week (35-40 mg/m²)	56 (26.3)
Once every 21 days (75-100 mg/m²)	12 (5.6)

CRT: Chemoradiotherapy; IMRT: Intensity-modulated radiotherapy; RT: Radiotherapy; SIB: Simultaneous integrated boost

Cut-off Values of Inflammatory Markers and Grouping with Hemoglobin Levels

ROC analysis determined the optimal cut-off values of NLR, PLR, and SII to predict survival as 2.34 (area under the curve (AUC):0.608, sensitivity 64%, specificity 53%, p=0.018), 122 (AUC:0.624, sensitivity 66%, specificity 54%, p=0.007) and 564 (AUC:0.631, sensitivity 70%, specificity 55%, p=0.004), respectively (**Figure 1**). According to these determined threshold values, the patients were categorized into two groups: low and high. According to these determined threshold values, the patients were categorized into two groups: low and high. The threshold values used to estimate the relationship between each inflammatory index and OS were also used for DFS and LRRFS, as in the study of Cho et al.[21]

Patients with high PLR and SII tended to have a more advanced T classification and stage than those in the low PLR and SII groups (p=0.007, p=0.004; p=0.016, p=0.018), and patients with high PLR also had an advanced stage of N (p=0.009). Patients over 60 years of age were mostly detected in the high NLR group (p=0.040). The presence of PNI was found more frequently in the high SII group (p=0.010), and subglottic extension was more common in both the high SII and high PLR groups (p=0.022, p=0.010). The relationship between clinicopathological features and NLR, PLR, and SII is detailed in **Table 2**.

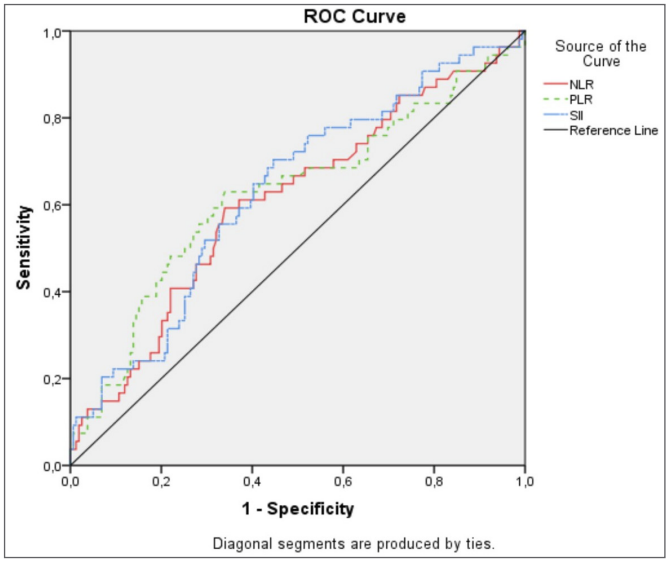

Figure 1. Receiver operating characteristic (ROC) curve analysis for NLR, PLR and SII

Table 2. The relationship with clinicopathological features and NLR, PLR and SII

Variable	NLR			PLR			SII		
	<2.34 102 (n,%)	≥2.34 111 (n,%)	p	<122 100 (n,%)	≥122 113 (n,%)	p	<564 100 (n,%)	≥564 113 (n,%)	p
Age									
<60	53 (55.8)	42 (44.2)	0.040	48 (50.5)	43 (49.5)	0.408	51 (53.7)	44 (46.3)	0.097
≥60	49 (41.5)	69 (58.5)		52 (44.1)	66 (55.9)		49 (41.5)	69 (58.5)	
Gender									
Female	0 (0)	4 (100)	0.053	2 (50)	2 (50)	0.902	1 (25)	3 (75)	0.375
Male	102 (48.8)	107 (51.2)		98 (46.9)	111 (53.1)		99 (47.1)	110 (52.6)	
Anterior commissura invasion									
-	21 (33.9)	41 (66.1)	0.063	21 (33.9)	41 (66.1)	0.260	21 (33.9)	41 (66.1)	0.135
+	29 (51.8)	27 (48.2)		25 (44.6)	31 (55.4)		27 (48.2)	29 (51.8)	
Subglottic extension									
-	43 (46.2)	50 (53.8)	0.116	42 (45.2)	51 (54.8)	0.010	43 (46.2)	50 (53.8)	0.022
+	7 (28)	18 (72)		4 (16)	21 (84)		5 (20)	20 (80)	
T stage									
T1-2	67 (51.5)	63 (48.5)	0.207	71 (54.6)	59 (45.4)	0.007	70 (53.8)	60 (46.2)	0.016
T3-4	35 (42.2)	48 (57.8)		29 (34.9)	54 (65.1)		30 (36.1)	53 (63.9)	
N stage									
N0-1	90 (48.9)	94 (51.1)	0.550	93 (50.5)	91 (49.5)	0.009	90 (48.9)	94 (51.1)	0.166
N2-3	12 (41.4)	17 (58.6)		7 (24.1)	22 (75.9)		10 (34.5)	19 (65.5)	
Stage									
1-2	62 (50.8)	60 (49.2)	0.335	68 (55.7)	54 (44.3)	0.004	66 (54.1)	56 (45.9)	0.018
3-4	40 (44)	51 (56)		32 (35.2)	59 (64.8)		34 (37.4)	57 (62.6)	
Lymphovascular invasion									
-	10 (55.6)	8 (44.4)	0.777	9 (50)	9 (50)	0.061	9 (50)	9 (50)	0.255
+	18 (50)	18 (50)		8 (22.2)	28 (77.8)		12 (33.3)	24 (66.7)	
Perineural invasion									
-	20 (46.5)	23 (53.5)	0.179	12 (27.9)	31 (72.1)	0.263	13 (30.2)	30 (69.8)	0.010
+	8 (72.7)	3 (27.3)		5 (45.5)	6 (54.5)		8 (72.7)	3 (27.3)	
Extracapsular extension									
-	25 (52.1)	23 (47.9)	0.923	15 (31.3)	33 (68.8)	0.917	18 (37.5)	30 (62.5)	0.667
+	3 (50)	3 (50)		3 (33.3)	4 (66.7)		3 (50)	3 (50)	

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

On the other hand, as in the study of Sung et al.,[22] three groups were formed according to each inflammatory index and Hb level (13 g/dL). In brief, patients were grouped as follows for NLR: Group ANLR, NLR <2.34 and Hb ≥13 g/dL; Group BNLR, NLR <2.34 and Hb <13 g/dL or NLR ≥2.34 and Hb≥13 g/dL; Group CNLR, NLR ≥2.34 and Hb <13 g/dL. Patients were grouped as follows for PLR: Group APLR, PLR <122 and Hb ≥13 g/dL; Group BPLR, PLR <122 and Hb <13 g/dL or PLR ≥122 and Hb ≥13 g/dL; Group CPLR, PLR ≥122 and Hb<13 g/dL. Patients were grouped as follows for SII: Group ASII, SII <564 and Hb ≥13 g/dL; Group BSII, SII <564 and Hb <13 g/dL or SII ≥564 and Hb ≥13 g/dL; Group CSII, SII ≥564 and Hb <13 g/dL.

Factors that Affect Overall Survival

With a median follow-up of 31 (5-79) months, the 5-y OS was 68.9% for all patients. The 5-y OS was significantly better in patients with the low NLR, PLR and SII groups, compared to patients with the high NLR, PLR and SII groups, with ratios 76.8% vs 60.7%; 77.7% vs 60.6%; and 83.1% vs 58.1%, respectively (p=0.008, p=0.014, p=0.001) (**Tables 3** and **4**).

The 5-y OS rates for groups ANLR, BNLR, and CNLR were 81.7%, 65.7%, and 49.6%; for groups APLR, BPLR, and CPLR were 79.8%, 70.7, and 51.1%; for groups ASII, BSII, and CSII were 83.1%, 65.7%, and 48.4%, respectively, and there was a significant difference between the groups (p=0.001, p=0.005, p=0.001) (**Table 3** and **4**). A significant survival difference was observed between group A patients compared to Group B and C patients (p=0.006, p<0.001; p=0.003, p<0.001) for NLR and SII subgroups, but the difference was significant between groups A and C, but not with group B for PLR (p=0.001; p=0.035).

In terms of clinicopathological parameters, age (p< 0.001), T stage (p=0.010), N stage (p<0.001), stage (p=0.005), anemia (p=0.004) were found statistically significant in univariate analysis (Tables 3 and 4). However, the multivariate analysis demonstrated that age (HR=3.89, 95% CI: 2.05-7.39, p<0.001), N stage (HR=3.33, 95% CI: 1.63-6.83, p=0.001), NLR (HR=1.85, 95% CI: 1.05-3.28, p=0.033), and NLR with Hb (HR=2.61, 95% CI: 1.14-5.97, p=0.022) were independent prognostic factors of OS in LSCC patients (**Table 3**, **Figure 2**).

Factors that Affect Disease Free Survival

The 5-y DFS was 61.5% for all patients. Patients with high NLR, PLR, and SII had lower DFS than those with low NLR, PLR, and SII (p=0.003, p=0.022, p=0.001), indicating that high NLR, PLR, and SII are significantly worse prognostic factors for DFS (**Table 3**). 5-y DFS rates were 71.5% vs 50.9%, 71% vs 52.3%, and 73.4% vs 50.1% for low and high groups, respectively (**Table 4**). Also, improved DFS rates were demonstrated in patients in the groups ANLR, APLR, and ASII (p=0.001, p=0.013, p=0.001), as presented in **Table 4** (**Figure 3**).

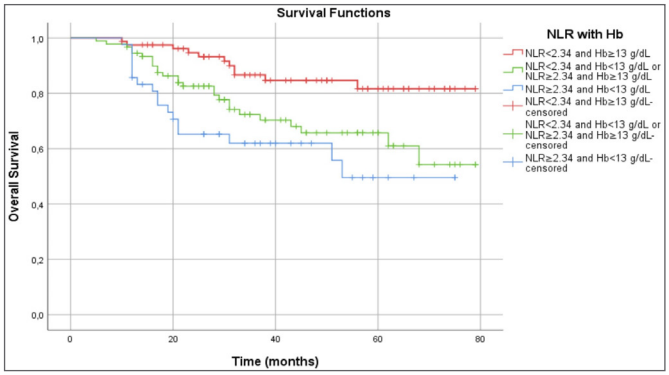

Figure 2. Kaplan-Meier graph of OS according to NLR with Hb

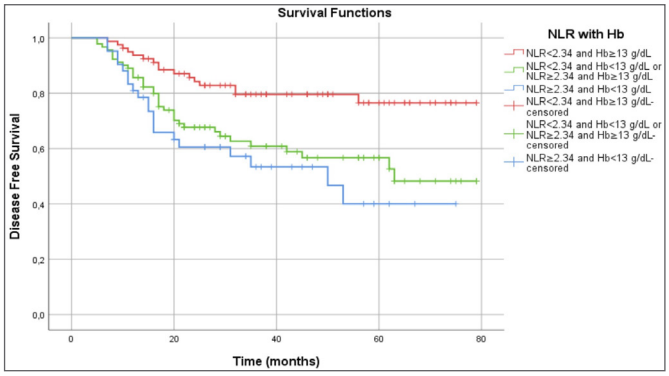

Figure 3. Kaplan-Meier graph of DFS according to NLR with Hb

Furthermore, age (p=0.001), T stage (p=0.011), N stage (p<0.001), stage (p=0.010), and anemia (p=0.016) were associated clinicopathological parameters with DFS in univariate analysis (Table 3). In multivariate analysis, age (HR=2.58, 95%CI: 1.54-4.31, p<0.001), N stage (HR=3.19, 95%CI: 1.80-5.66, p<0.001), NLR (HR=1.81, 95%CI: 1.11-2.96, p=0.017), and NLR with Hb (HR=3.32, 95%CI: 1.20-9.16, p=0.028) remained as prognostic for DFS (**Table 3**).

Factors that Affect Local Regional Recurrence Free Survival

The 5-y LRRFS was 62.4% for all patients. As presented in Table 4, increased LRRFS rates were found in patients with low NLR and SII groups (p=0.008, p=0.002). Also, improved LRRFS rates were demonstrated in patients in the groups ANLR and ASII (p=0.003, p=0.002) (**Table 4**, **Figure 4**).

Age (p<0.001) and N stage (p=0.001) were significant clinicopathological factors affecting LRRFS in univariate analysis (**Table 3**). In multivariate analysis, age (HR=2.78, 95%CI: 1.61-4.79, p<0.001) and N stage (HR=2.87, 95%CI: 1.63-5.05, p<0.001) remained as prognostic for LRRFS.

Table 3. Univariate and multivariate cox regression analysis for overall survival, disease free survival and local regional recurrence free survival

Variable	OS Univariate		DFS Univariate		LRRFS Univariate	
	HR (95% Cl)	p	HR (95% Cl)	p	HR (95% Cl)	p
Age <60 vs ≥60	3.40 (1.81-6.38)	<0.001	2.34 (1.41-3.88)	0.001	2.66 (1.56-4.55)	<0.001
Gender Female vs male	1.00 (0.13-7.31)	0.993	0.66 (0.16-2.73)	0.570	0.61 (0.15-2.52)	0.494
Anterior commissura invasion -/+	1.06 (0.45-2.52)	0.884	0.86 (0.42-1.75)	0.681	0.73 (0.34-1.55)	0.415
Subglottic extension -/+	0.59 (0.23-1.55)	0.286	0.88 (0.37-2.05)	0.768	0.79 (0.33-1.87)	0.592
T stage T1-2 vs T3-4	1.98 (1.16-3.40)	0.010	1.80 (1.13-2.86)	0.011	1.50 (0.93-2.40)	0.089
N Stage N0-1 vs N2-3	3.35 (1.86-6.02)	<0.001	3.15 (1.87-5.29)	<0.001	2.51 (1.44-4.36)	0.001
Stage 1-2 vs 3-4	2.13 (1.23-3.69)	0.005	1.81 (1.14-2.90)	0.010	1.53 (0.94-2.48)	0.077
LVI No vs Yes	2.19 (0.62-7.70)	0.220	2.96 (0.86-10.18)	0.084	2.48 (0.71-8.65)	0.153
PNI No vs Yes	0.22 (0.03-1.71)	0.151	0.38 (0.08-1.67)	0.205	0.21 (0.02-1.58)	0.131
ECE No vs Yes	1.43 (0.32-6.32)	0.637	1.92 (0.55-6.64)	0.301	1.27 (0.29-5.61)	0.746
Hemoglobin ≥13 vs <13	0.46 (0.27-0.80)	0.004	0.56 (0.35-0.90)	0.016	0.63 (0.39-1.04)	0.070
NLR <2.34 vs ≥2.34	2.08 (1.19-3.66)	0.008	2.02 (1.24-3.28)	0.003	1.93 (1.17-3.18)	0.008
PLR <122 vs ≥122	2.00 (1.13-3.53)	0.014	1.73 (1.07-2.81)	0.022	1.62 (0.99-2.67)	0.050
SII <564 vs ≥564	2.56 (1.39-4.51)	0.001	2.31 (1.40-3.81)	0.001	2.19 (1.31-3.66)	0.002
NLR with Hb	1.47 (1.18-1.84)	0.001	1.38 (1.14-1.67)	0.001	1.30 (1.06-1.59)	0.003
Group A vs B		0.006		0.003		0.002
Group A vs C		<0.001		<0.001		0.005
Group B vs C		0.145		0.321		0.846
PLR with Hb	1.40 (1.13-1.73)	0.005	1.29 (1.07-1.56)	0.013	1.22 (1.00-1.49)	0.040
Group A vs B		0.035		0.031		0.025
Group A vs C		0.001		0.005		0.026
Group B vs C		0.160		0.358		0.835
SII with Hb	1.48 (1.19-1.84)	0.001	1.38 (1.14-1.67)	0.001	1.30 (1.07-1.59)	0.002
Group A vs B		0.003		0.001		0.001
Group A vs C		<0.001		<0.001		0.002
Group B vs C		0.190		0.405		0.926
	Multivariate		**Multivariate**		**Multivariate**	
	HR (%95 Cl)	**p**	**HR (%95 Cl)**	**p**	**HR (%95 Cl)**	**p**
Age <60 vs ≥60	3.89 (2.05-7.39)	<0.001	2.58 (1.54-4.31)	<0.001	2.78 (1.61-4.79)	<0.001
N Stage N0-1 vs N2-3	3.33 (1.63-6.83)	0.001	3.19 (1.80-5.66)	<0.001	2.87 (1.63-5.05)	<0.001
NLR <2.34 vs ≥2.34	1.85 (1.05-3.28)	0.033	1.81 (1.11-2.96)	0.017	1.66 (0.98-2.82)	0.056
NLR with Hb	2.61 (1.14-5.97)	0.022	3.32 (1.20-9.16)	0.028	1.85 (0.85-4.01)	0.116
Group A vs B		0.056		0.013		
Group A vs C		0.006		0.021		

CI: Confidence interval; DFS: Disease free survival; ECE: Extracapsular extension; Hb: Hemoglobin; HR: Hazard ratio; LRRFS: Local regional recurrence free survival; LVI: Lymphovascular invasion; OS: Overall survival; PNI: Perineural invasion; RT: Radiotherapy. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

Table 4. Survival outcomes according to NLR, PLR, SII and Hb level

		NLR		PLR		SII		Hb		NLR with Hb			PLR with Hb			SII with Hb		
		NLR <2.34	NLR ≥2.34	PLR <122	PLR ≥122	SII <564	SII ≥564	Hb ≥13	Hb <13	Group ANLR	Group BNLR	Group CNLR	Group APLR	Group BPLR	Group CPLR	Group ASII	Group BSII	Group CSII
OS	Median, (months) 95% CI	NR	68 -	NR	NR	NR	68 -	NR	NR	NR	NR	53 -	NR	NR	NR	NR	NR	53 -
	2-y	90.7	77.2	89.7	78.4	90.7	77.4	89.4	70.1	94.7	82.6	65.2	92.6	83	68.9	94.8	81.1	68.3
	5-y	76.8	60.7	77.7	60.6	83.1	58.1	75.1	55.1	81.7	65.7	49.6	79.8	70.7	51.1	83.1	65.7	48.4
	p	0.008		0.014		0.001		0.004			0.001			0.005			0.001	
DFS	Median, (months) 95% CI	NR	62 (45.93-78.06)	NR	62 (40.45-80.54)	NR	62 (42.75-81.24)	NR	53 -	NR	63 -	50 (25.91-74.10)	NR	63	50 (21.79-78.20)	NR	63	50 (23.91-76.09)
	2-y	79.6	66.1	78.3	67.3	83.5	62.6	76.8	62.3	84.3	67.7	60.6	81.4	69.2	62.4	86.3	63.8	61.1
	5-y	71.5	50.9	71	52.3	73.4	50.1	67.7	47.7	76.5	56.7	40	73.8	58.5	44	76.8	57.9	40.3
	p	0.003		0.022		0.001		0.016			0.001			0.013			0.001	
LRRFS	Median, (months) 95% CI	NR	62 (43.68-80.31)	NR	68 -	NR	62 (39.5-84.47)	NR	NR	NR	68 (35.10-100.89)	53 -	NR	68 -	NR	NR	68 -	53 -
	2-y	80.4	68.8	80.3	69.2	84.5	65.2	78.5	64.8	85.4	69.2	64.3	83.7	69.8	65.9	89.6	65.3	65
	5-y	71.9	51.4	70.8	54.5	73.6	51.4	67.1	52.3	77.2	54.7	47.4	73.5	58.1	50.3	77	56.7	47.2
	p	0.008		0.050		0.002		0.070			0.003			0.040			0.002	

CI: Confidence interval; DFS: Disease free survival; Hb: Hemoglobin; LRRFS: Local regional recurrence free survival; NLR: Neutrophil-to-lymphocyte ratio; NR: Not reached; OS: Overall survival; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

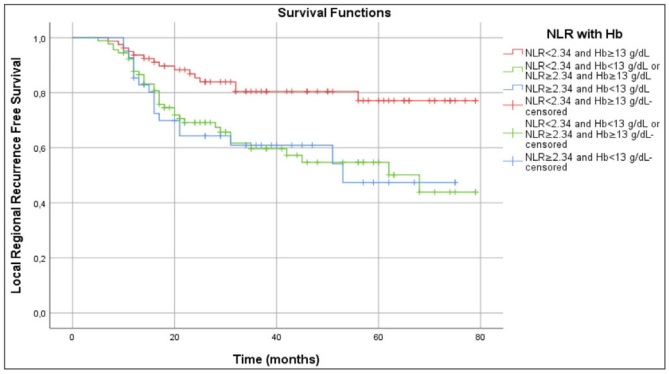

Figure 4. Kaplan-Meier graph of LRRFS according to NLR with Hb

DISCUSSION

In this study, we investigated whether hematological parameters have a prognostic effect on survival in patients with LSCC treated with RT. Our findings demonstrated that high levels of pretreatment NLR, PLR, and SII and low Hb levels were associated with worse survival (except for PLR and Hb for LRRFS) in univariate analysis. In addition, the analysis of the subgroups determined according to Hb level and inflammatory indices showed that survival was significantly better in patients in each group A with low inflammatory index and high Hb. In the multivariate analysis, high NLR and group CNLR were statistically significant predictors of worse OS and DFS. We found that the predictive ability increased even more when the inflammatory index was combined with the Hb level.

Over the past decades, systemic inflammation indices have been extensively investigated for patient classification and survival prediction in various tumor types.[14-16] NLR, PLR and SII have been shown to predict survival in many studies and reliable results have been obtained with meta-analyses, but fewer studies have been reported in terms of LSCC.[14-16,20,23,24] Currently available data include retrospective studies of systemic inflammation indices such as NLR, PLR, and SII in LSCC. Surgery was used as the treatment option in most of these series, and survival outcomes were associated with surgery. For example, Fu et al.[23] reported that preoperative NLR was correlated with survival in a retrospective series of 420 advanced LSCC patients who underwent total laryngectomy, with a hazard ratio of 1.42. The threshold for NLR was 2.59, with 5 y-OS 63% in the low NLR group and 52.8% in the high NLR group. In the large series of Mao et al.[24] patients were divided into three subgroups according to their PLR scores as low (119.55), moderate (>119.55 and 193.55), and high (>193.55). The 5-y cancer specific survival rates were found to be 75.3%, 68.4%, and 53.9%, respectively, according to the groups. The 5-y-survival rates found in these two studies are similar to ours study in terms of NLR and PLR. In these series, adjuvant RT was probably given after surgery based on the pathological characteristics of the patients but was not specified in the methodology of these studies. In some

studies, in which systemic inflammatory indices were evaluated preoperatively, it was stated that adjuvant RT/CRT was applied to some of the patients. Although the number of patients was not high, in the study published by Li et al.[24] in 2021, approximately two-thirds of the 147 patients underwent adjuvant RT. In this study, NLR, PLR, and SII were evaluated together; the 5 y- OS rates were 79.7% vs 36.4%, 70.5% vs 28.8%, and 72.2% vs 29.6% for the low and high groups; the 5 y- PFS rates were 71.2% vs 31.9%, 64.8% vs 22%, and 65% vs 25%, respectively. It was shown that preoperative NLR, PLR, and SII contributed significantly to both OS and progression free survival (PFS).

Studies investigating the effect of systemic inflammatory index on survival in patients undergoing definitive RT in LSCC were mostly mentioned in the HNC studies. Bojaxhiu et al.[26] reported that high NLR is an indicator of poor OS in patients with HNC using RT as the main treatment modality, and this predictive feature was still valid for LSCC when subgroup analysis was performed by site of primary disease. Similar to the results of other studies, NLR was found to be predictive for OS and PFS in a series of 125 advanced-stage patients undergoing definitive CRT (HR: 1.51; HR: 1.79).[27] Cho et al.[21] evaluated the outcomes of 621 patients and reported that 5 y- OS (83.8% vs 50.9%) and PFS (75.8 vs 39.2%) were better in the low NLR group in HNC. More recently, high NLR values in LSCC have been shown to be associated with reduced OS, DFS, and PFS, based on the results of a published meta-analysis involving 12 retrospectively designed 3710 patients undergoing surgery and/or RT (HR:1.76; HR:1.66; HR:1.72).[20]

In our study, while most of the patients were treated with definitive RT/CRT, adjuvant RT/CRT was applied in to approximately one-fourth of them. Since it would be more accurate to compare the results of studies designed similarly to our study, we focused on studies that included patients who underwent definitive RT and patients who received RT after surgery. Atasever Akkas et al.[28] evaluated 118 patients; the 5 y- OS rates were 69% vs 41%, 64% vs 55%, and 76% vs 34% for the low and high groups; the 5 y- DFS rates were 69% vs 35%, 64% vs 49%, and 69% vs 33%, respectively. They found a relationship between NLR, PLR, and SII and survival in patients with LSCC in the univariate analysis, while SII was significantly correlated with OS in the multivariate analysis (HR:10.54). Recently, Kotha et al.[29] showed that high NLR is a poor prognostic marker for OS and cause specific survival in a more homogeneous group of 1047 patients with advanced-stage disease (HR: 1.31; HR: 1.46). In our study, NLR, PLR, and SII were associated with both OS, DFS, and LRRFS (excluding PLR) in univariate analysis, but only NLR remained significant for OS and DFS in multivariate analysis. As mentioned above, regardless of the type of treatment, it was observed that prognostically significant results were obtained with NLR, as in our study, and in most of the studies.

As in other cancers, the threshold values determined for systemic immune inflammation biomarkers in studies reported for LSCC are specific to each study and cannot be used or valid in any other study. Currently, it is not known which values should be accepted as reference points for these markers, but their predictive effect is evident.

As a result of experimental and clinical studies, it is known that tumor hypoxia and anemia negatively affect the efficacy of RT in solid tumors, including HNC.[30] Years ago, in a randomized study to examine the radiosensitizing effect of Misonidazole, it was determined that high Hb levels increased local control rates, especially in hypopharyngeal cancer.[21] Subsequent studies have reported lower recurrence-free survival rates for LSCC in patients with anemia before and/or after RT compared to those without.[32-34] In addition, in another study evaluating the difference between the Hb levels detected preoperatively, pre-RT, and during RT, it was shown that OS was adversely affected by the decline of Hb levels during RT.[35]

Although the accepted threshold value for anemia varied in the aforementioned studies, 12-14.5 g/dl was preferred in males. In our study, which was dominated by male patients, we accepted values below 13 g/dl as anemia. Consistent with the literature, we found that anemia was associated with a shorter OS as well as DFS. In order to evaluate the hypothesis whether the predictive effect can be strengthened by combining low Hb level, we further categorized the patients into three groups for each inflammatory index. When we reanalyzed according to these groups, we found that the predictive effect was increased when NLR was combined with Hb in multivariate analysis.

Recent data have demonstrated the prognostic impact of systemic inflammatory indices, which are not yet used in risk scoring. In a retrospective study, Pogorzelski et al.[36] aimed to evaluate chemotherapy response and survival in metastatic HNC and presented their data on prognostic scoring, which they defined using NLR, Hb, age, and ECOG performance status parameters, which they found statistically significant in multivariate analyzses. The median value determined for each value in the patients included in the study was accepted as the threshold value for NLR, Hb, and age. High NLR, low Hb, advanced age, and poor performance were each determined as positive factors, and prognostic scores from 0 to 4 were defined by summing them numerically. It was found that OS and PFS were shortened in patients with a high prognostic clinical score. In our study, we grouped patients by combining Hb level and systemic inflammatory index without considering other parameters, and the best OS and DFS were detected in the group with both low NLR and high Hb levels.

Studies evaluating the combined prognostic effect of hematological parameters obtained from routine blood samples are few in LSCC. In a series of 68 patients with LSCC who underwent induction chemotherapy, the effect of Hb and NLR values at the beginning and at the end of treatment on both response to chemotherapy and survival was investigated.[37] In this study, the authors evaluated parameters separately. Anemia or high NLR at baseline did not alter chemotherapy response but worsened OS. Similarly, when hematological parameters were evaluated separately in our study, it was shown that survival decreased with anemia and high systemic inflammatory index.

The Hb level was added to the inflammatory indices in Hb, albumin, lymphocyte, platelet (HALP) score, which is thought to reflect the immune and nutritional status. There are meta-analyses showing that a low HALP score is associated with reduced survival in solid tumors, but no study involving HNC has yet been identified.[38,39]

The strengths of this study are as follows. In our study, systemic inflammatory indices such as NLR, PLR, and SII were evaluated together. Since studies on systemic inflammatory indices in LSCC are few, we have contributed to the literature by obtaining significant results with a relatively large number of patients. The effect of Hb level, which had a previously proven predictive effect, was also investigated. In addition, we were able to show that the prognostic efficiency of hematological parameters increased when patients were divided into groups by combining both hematological parameters.

However, this study had several limitations. First, the data were collected retrospectively, and all patients were treated at a single institution. Second, the patients in our cohort consisted of a highly heterogeneous group with based on the stage and the different treatment options applied. Third, because of its retrospective design, it was difficult to accurately determine whether patients were taking drugs that could alter hematological parameters, such as statins, nonsteroidal anti-inflammatory drugs, or iron supplements. Therefore, prospective studies will be more helpful in revealing the prognostic effect of hematological parameters on survival with a more homogeneous patient population in LSCC.

CONCLUSION

According to the results of our study, the predictive ability increased, even more, when the NLR was combined with the Hb level. The development of straightforward and reliable prognostic markers is essential to validate hematological parameters for patient risk stratification, response to therapy, and prediction of survival.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No: 10/11)

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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