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The Predictive Role of Inflammatory Biomarkers in Patients With Larynx Cancer Undergoing Definitive Radiotherapy

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Abstract

Inflammation plays an important role in the process of cancer development. The number of studies evaluating the ability of inflammatory biomarkers to predict survival has increased in recent years. This study aimed to comprehensively evaluate the predictive role of inflammatory biomarkers in patients with larynx cancer undergoing definitive radiotherapy. A total of 101 patients who underwent definitive radiotherapy for larynx cancer at our center were retrospectively examined. Blood samples were taken from the patients before radiotherapy to obtain biomarkers such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), pan-immune inflammatory value (PIV), hemo-eosinophil inflammation index (HEI), albumin, and Lactate dehydrogenase (LDH). The study examined the predictive value of parameters for progression-free survival (PFS), local recurrence-free survival (LRFS), and overall survival (OS) using both univariate and multivariate Cox regression analysis. In the univariate analysis, the biomarkers that predicted PFS were SII, PIV, CRP, and Eastern Cooperative Oncology Group Performance Status (ECOG PS). According to the multivariate analysis, only CRP was found to be a significant predictor of PFS. In the univariate analysis, the following biomarkers were found to predict OS: NLR, PLR, MLR, SII, PIV, CRP, HEI, stage, and ECOG PS. In the multivariate analysis, NLR and ECOG PS were found to be predictors of OS. A significant difference was found in MLR, PIV, and CRP values based on the presence of lymphatic metastasis. The current study is the first to comprehensively examine the relationship between larynx cancer and several inflammatory biomarkers. Many of these biomarkers have been shown to predict both PFS and OS in patients with larynx cancer undergoing definitive radiotherapy. It has been shown that PIV and CRP may predict the presence of lymphatic metastases in addition to PFS and OS.

Keywords

larynx cancer, radiotherapy, inflammation, biomarkers, prediction

Abbreviations

CRP, C-reactive protein; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; MLR, Monocyte-lymphocyte ratio; SII, Systemic immune-inflammation index; PIV, Pan-immune inflammatory value; HEI, Hemo-eosinophil inflammation index; LDH, Lactate dehydrogenase; ROC, Receiver Operating Characteristic; PFS, Progression-free survival; LRFS, Local recurrence-free survival; OS, Overall survival; ECOG, PS Eastern Cooperative Oncology Group Performance Status; MRI, Magnetic Resonance Imaging; PET/CT, Positron Emission Tomography/Computed Tomography; IMRT, Intensity-modulated radiotherapy; AUC, Area under the curve; CI, Confidence interval.

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Introduction

Squamous cell carcinoma of the head and neck is the sixth most commonly seen cancer in all countries, and larynx cancer constitutes a fifth of all head and neck cancers.[1,2] Larynx cancer is primarily caused by smoking and alcohol consumption, which are considered the fundamental risk factors associated with

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this disease.[3] While 5-year survival rates reach 90% in patients with T1-2 N0 larynx cancer, this rate falls dramatically in advanced stage larynx cancer.[4] Patient-related prognostic factors include age, gender, performance status, nutritional status, and social factors. Tumor-related prognostic factors include stage, tumor localization, histology, and tumor markers.[5]

In the process of cancer development, there is an interaction between cancer cells and immune cells. This interaction can result in either cancer cell suppression or proliferation.[6] The cascade of events associated with chronic inflammation encompasses the sequential emergence of metaplasia, dysplasia, and neoplasia.[7] Subsequent to inflammation induced by tumors, a series of consequential events transpire, including the inhibition of apoptosis, facilitation of angiogenesis, and DNA damage.[8,9] The genesis of cancer is predominantly attributable to DNA damage, notably stemming from reactive oxygen and nitrogen derivatives. These products are expressed from inflammatory cells and epithelial cells under chronic inflammation.[10]

The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) are commonly used as biomarkers of inflammation. These biomarkers are low-cost and easily available, and their prognostic value has been investigated in lung cancer, colorectal cancer, and hepatocellular cancer.[11–13] Other than these biomarkers, studies of new biomarkers have been conducted and their predictive role in various cancers continues to be investigated. The pan-immune inflammation value (PIV) has demonstrated a strong predictive value compared to traditional biomarkers in patients with metastatic colorectal cancer.[14] The systemic immune-inflammation index (SII) obtained from lymphocyte, platelet, and neutrophil counts in blood has significant prognostic value in esophageal, colorectal, and small-cell lung cancer.[15] However, variability in biomarker levels due to comorbidities and lack of standardization poses significant challenges. Additionally, limited clinical validation and integration with existing protocols remain substantial barriers to their widespread adoption in clinical practice. Therefore, ongoing comprehensive research and collaborative efforts are essential to overcome these obstacles and fully harness the potential of inflammatory biomarkers in cancer prognosis.

This study aimed to comprehensively examine the predictive value of inflammatory biomarkers such as NLR, PLR, MLR, SII, PIV, hemo-eosinophil index (HEI), albumin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) in patients with larynx cancer receiving definitive radiotherapy.

Material and Method

Patient Selection

Approval for this study was granted by the Clinical Research Ethics Committee of the Akdeniz University Medical Faculty. In this single-center, retrospective study, data from patients with larynx squamous cell carcinoma who received curative treatment at the University Medical Faculty Hospital between January 2014 and December 2022 were examined. Patients with severe comorbidities leading to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3–4, as well as those with other histopathologies, incomplete medical records, distant metastasis, prior primary surgery, or non-curative treatment, were excluded. Additionally, conditions known to elicit either an acute or chronic systemic inflammatory response, such as infections and chronic active inflammatory diseases, were excluded. This retrospective study followed the relevant REMARK guidelines.[16] All patient data were deidentified.

Treatment Details and Follow-up Procedures

No changes were made to patients' treatment or follow-up procedures for the purposes of this study. The clinical procedures adhered to are outlined as follows. Patients received definitive radiotherapy at doses ranging from 63 Gy to 70 Gy based on tumor stage. The radiotherapy techniques chosen were intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy. A total of 64 patients (63.4%) administered concurrent systemic treatment, 52 of whom received cisplatin and 12 of whom received cetuximab. After the end of primary treatments, patients were assessed every 3–6 months during the first 2 years and every 6–12 months during the following 3 years. During patient follow-up, physical examination, laryngoscopic examination, MRI, and PET/CT were performed.

Data Collection

The hospital records were used to collect data on age, gender, ECOG PS, histopathologies, tumor stage, and inflammatory biomarkers. Blood samples were taken to obtain inflammatory biomarkers within one month before radiotherapy. The patients were staged with Magnetic Resonance Imaging (MRI) and Positron Emission Tomography/Computed Tomography (PET/CT) at the time of diagnosis, using the NCCN Guidelines version 1.2024.

The biochemical data of CRP (mg/L), albumin (g/dL), and LDH (U/L) were collected. The NLR was calculated as neutrophil count (10^3 /mL) / lymphocyte count (10^3 /mL), the PLR as platelet count (10^3 /mL) / lymphocyte count (10^3 /mL), the MLR as monocyte count (10^3 /mL) / lymphocyte count (10^3 /mL), the SII as neutrophil count (10^3 /mL) x platelet count (10^3 /mL)) / lymphocyte count (10^3 /mL), and the PIV as neutrophil count (10^3 /mL) x platelet count (10^3 /mL) x monocyte count (10^3 /mL) / lymphocyte count (10^3 /mL).

HEI was calculated using the criteria of hemoglobin < 12 g/dL, SII > 560, and eosinophil count $\geq 100/\mu L$. Those with 0–1 points were considered low risk, and those with 2–3 points were considered high risk. The calculator used can be found at the link https://casadeigardini.wixsite.com/heiindex.[17]

Statistical Analysis

Power analysis was performed with the G-power tool and post hoc power analysis showed that the sample size ($N = 101$) was

adequate to detect the high effects (f = 0.6, P ≤ 0.05, power = 0.83).

Statistical analyses were performed using IBM SPSS version 24.0 software (IBM Corp. 2016, Armonk, NY, USA) and a value of $p < 0.05$ was considered statistically significant. Descriptive statistics were used to identify the patient characteristics. The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to determine whether the distribution of the parameters was normal. To assess whether there is a difference in biomarker levels between groups with and without lymph node metastasis, Student's t-test was performed for biomarkers meeting the normality assumption, and Mann-Whitney U test was done for those not meeting the normality assumption. The cut-off values of the biomarkers were determined from receiver operating characteristic (ROC) analysis using the criterion that identifies the cut-off value at the point where sensitivity is closest to specificity.[18]

Overall survival (OS) is defined as the period from the date of the diagnosis of larynx cancer to the date of death from any cause or the last follow-up. Progression-free survival (PFS) is defined as the time from diagnosis to disease progression or death from any cause without disease progression. Local recurrence-free survival (LRFS) is defined as the time from diagnosis to local recurrence or death from any cause without local recurrence. If the patient was still alive and had not experienced any progression or local recurrence, PFS and LRFS data were recorded once confirmation of the absence of progression and local recurrence was obtained. Survival curves were generated using the Kaplan-Meier method, and differences between the curves were analyzed using the log-rank test. Univariate Cox proportional hazards regression analyses were used to estimate the hazard ratio for PFS, LRFS, and OS. After conducting univariate analyses, variables with statistical significance ($p < 0.05$) were included in the multivariate analysis. The hazard risk of individual factors was estimated using hazard ratio (HR) with a 95% confidence interval (CI).

Results

The patient characteristics are presented in Table 1. Most of the patients (56.4%) were aged ≤65 years and the vast majority (92.1%) were male. The stages at the time of diagnosis were Stage 1 in 19 (18.8%) patients, Stage 2 in 20 (19.8%), Stage 3 in 18 (17.8%), Stage 4A in 40 (39.6%), and Stage 4B in 4 (4.0%). The ECOG-PS score was 0–1 in 89 (88.1%) patients and 2 in 12 (11.9%). More patients received chemoradiotherapy than radiotherapy alone (63.4% vs 36.6%). Radiotherapy was administered at a dose of 63 Gy to 8 (7.9%) patients, at 65.25 Gy to 14 (13.9%) at 70 Gy to 66 (65.3%), and at other doses to 13 (12.9%). According to the HEI value, 61 (60.4%) patients were classified as high-risk and 40 (39.6%) as low-risk. The median follow-up period of patients was 23 months (range, 2.9-112 months).

Cut-off values were determined using ROC curve analysis (Table 2). The cut-off value for NLR was 2.61 with 72.2% sensitivity and 72.3% specificity; for PLR, it was 133.6 with 55.6% sensitivity and 55.4% specificity; for MLR, it was 0.33 with 61.1% sensitivity and 60% specificity; for SII, it was 656.5 with 61.1% sensitivity and 61.5% specificity; for PIV, it was 478.3 with 63.9% sensitivity and 64.6% specificity; for CRP, it was 6.6 mg/L with 67.6% sensitivity and 68.9% specificity; for LDH, it was 187.5 U/L with 55.9% sensitivity and 56.9% specificity; and for albumin, it was 4.27 g/dL with 51.4% sensitivity and 51.9% specificity.

Table 1. Patient Characteristics (n = 101).

Characteristic	n	%
Age (years)		
≤65	57	56.4
>65	44	43.6
Gender		
Female	8	7.9
Male	93	92.1
Stage		
Stage I	19	18.8
Stage II	20	19.8
Stage III	18	17.8
Stage IVA	40	39.6
Stage IVB	4	4.0
ECOG PS		
0–1	89	88.1
2	12	11.9
Treatment		
Only radiotherapy	37	36.6
Curative chemoradiotherapy	64	63.4
Total Radiation Dose		
63 Gy	8	7.9
65.25 Gy	14	13.9
70 Gy	66	65.3
Other	13	12.9
Hemo-Eosinophil Inflammation Index		
High risk	61	60.4
Low risk	40	39.6

ECOG PS, Eastern Cooperative Oncology Group-Performance Status.

One-year and two-year PFS rates were 87.9% and 73.8%, respectively. The effects of clinical characteristics and inflammatory biomarkers on PFS are presented in Table 3. In the univariate analysis, significant predictors of PFS were SII ($p = 0.039$), PIV ($p = 0.019$), CRP ($p < 0.001$), and ECOG PS ($p = 0.023$). The NLR, PLR, MLR, LDH, albumin, age, HEI, T-classification, stage, and lymphatic metastasis were shown not to significantly predict PFS in the univariate analysis. In the multivariate analysis, only CRP was identified as a statistically significant predictor of PFS ($p = 0.002$).

One-year and two-year LRFS rates were 90% and 78.9%, respectively. The effects of clinical characteristics and inflammatory biomarkers on LRFS are presented in Table 4. The univariate analysis demonstrated that only CRP ($p = 0.004$) significantly predicted LRFS. No significant effects of other variables on LRFS were detected.

One-year and two-year OS rates were 93.7% and 80.5%, respectively. The effects of clinical characteristics and inflammatory biomarkers on OS are given in Table 5. The analysis

Table 2. ROC Curve Analysis for the Prediction of Overall Survival.

Variable	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p value
NLR	2.61	72.2	72.3	0.74 (0.64–0.84)	< 0.001
PLR	133.6	55.6	55.4	0.62 (0.51–0.73)	0.038
MLR	0.33	61.1	60.0	0.63 (0.51–0.74)	0.029
SII	656.5	61.1	61.5	0.70 (0.60–0.81)	0.001
PIV	478.3	63.9	64.6	0.69 (0.59–0.80)	0.001
CRP	6.6	67.6	68.9	0.74 (0.64–0.84)	<0.001
LDH	187.5	55.9	56.9	0.63 (0.51–0.74)	0.035
Albumin	4.27	51.4	51.9	0.57 (0.45–0.69)	0.220

AUC, area under curve; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune inflammation value; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 3. Univariate and Multivariate Cox Regression Analysis for the Prediction of Progression-Free Survival.

		Univariate Analysis		Multivariate Analysis	
Variable	Cut-off	HR (%95 Cl)	p	HR (%95 Cl)	p
NLR	≤2.61 versus > 2.61	2.02 (0.94–4.35)	0.070		
PLR	≤133.6 versus > 133.6	1.41 (0.63–3.14)	0.391		
MLR	≤0.33 versus > 0.33	1.66 (0.75–3.66)	0.207		
SII	≤656.5 versus > 656.5	2.27 (1.04–4.95)	0.039	0.95 (0.36–2.52)	0.929
PIV	≤478.3 versus > 478.3	2.70 (1.18–6.19)	0.019	1.68 (0.61–4.57)	0.308
CRP	≤6.6 versus > 6.6	6.20 (2.29–16.7)	<0.001	5.03 (1.81–13.9)	0.002
LDH	≤187.5 versus > 187.5	1.25 (0.56–2.78)	0.580		
Albumin	≤4.27 versus > 4.27	0.70 (0.31–1.58)	0.401		
Age	≤65 versus > 65	1.30 (0.59–2.83)	0.506		
HEI	High versus Low	0.70 (0.31–1.58)	0.398		
T	1–2 versus 3–4	1.31 (0.61–2.79)	0.480		
Stage	I-II versus III-IV	1.42 (0.63–3.16)	0.392		
ECOG PS	0–1 versus 2	3.21 (1.17–8.83)	0.023	2.27 (0.75–6.82)	0.143
N	N + versus N0	0.86 (0.39–1.93)	0.731		

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune inflammation value, CRP, C-reactive protein; LDH, lactate dehydrogenase; HEI, Hemo-eosinophil inflammation index; ECOG PS, Eastern Cooperative Oncology Group-Performance Status; N, lymphatic metastasis.

revealed that several factors were significantly associated with OS. In the univariate analysis, significant predictors of OS were NLR ($p < 0.001$), PLR ($p = 0.036$), MLR ($p = 0.007$), SII ($p = 0.015$), PIV ($p < 0.001$), CRP ($p = 0.001$), HEI ($p = 0.025$), stage ($p = 0.019$), and ECOG PS ($p < 0.001$). LDH, albumin, age, T classification, and lymphatic metastasis were determined not to predict OS. In the multivariate analysis, statistically significant predictors of OS were found to be NLR ($p = 0.004$) and ECOG PS ($p = 0.005$). Additionally, in the multivariate analysis, CRP ($p = 0.083$) and PIV ($p = 0.121$) were close to statistical significance for OS. The predictive values of the NLR and PIV biomarkers for OS are illustrated in Figures 1 and 2, respectively.

The difference in inflammatory biomarkers between groups with and without lymphatic metastasis was examined. MLR levels were higher ($U = 849$, $z = -1.973$, $p = 0.04$) in patients with lymphatic metastasis (median, 0.40; range, 0.12 to 0.85) than in patients without lymphatic metastasis (median, 0.29; range, 0.01 to 0.75). Similarly, PIV values were higher ($U = 844$, $z = -2.013$, $p = 0.04$) in patients with lymphatic metastasis (median, 514.3; range, 132.6 to 3588.8) than in patients without lymphatic metastasis (median, 373.5; range, 131.0 to 1669.1). Additionally, CRP levels were significantly higher ($U = 737$, $z = -2.134$, $p = 0.03$) in patiens with lymphatic metastasis (median, 10.7; range, 0.5 to 83.5) than in patients without lymphatic metastasis (median, 5.6; range, 0.3 to 99.4).

Discussion

In this study, the effects of inflammatory biomarkers, such as NLR, PLR, MLR, SII, PIV, HEI, CRP, albumin, and LDH on PFS, LRFS, and OS in patients with larynx cancer who received definitive radiotherapy were examined. This is the first study in the literature to comprehensively examine the predictive role of inflammatory biomarkers in patients with larynx cancer who have undergone definitive radiotherapy. Moreover, our study is the first to evaluate the predictive role of PIV and HEI in patients with larynx cancer.

The role of inflammation in cancer is crucial. Inflammation is associated with tumors and their microenvironment, and systemic inflammation is linked to cytokines and inflammatory proteins. The presence of necrosis, inflammasomes, cytokines, chemokines, and transcription factors in the tumor micro-environment causes the growth and spread of the tumor. Inflammasomes are complex structures formed by NOD-like receptors and various proteins. They induce IL-1β, IL-18, and pyroptosis, creating an environment suitable for tumor development.[7,10]

Acute phase proteins, cytokines, and immune cells in circulation play a role in systemic inflammation.[19] In a study by Bouras et al, the relationship between genetic representations of cytokines in circulation and various cancers was examined using Mendelian randomization. There was determined to be a relationship between the genetic representations of cytokines such as MIF, MIG, and MCSF, and various cancers.[20] Contrary to popular belief, recent studies have shown that neutrophils contribute to the development and spread of tumors. Neutrophils express angiogenesis factors like MMP9 and VEGF, and

Table 4. Univariate Cox Regression Analysis for the Prediction of Local Recurrence-Free Survival.

		Univariate Analysis	
Variable	Cut-off	HR (%95 Cl)	p
NLR	≤2.61 versus > 2.61	1.66 (0.73–3.80)	0.224
PLR	≤133.6 versus > 133.6	1.16 (0.49–2.79)	0.725
MLR	≤0.33 versus > 0.33	1.72 (0.72–4.09)	0.216
SII	≤656.5 versus > 656.5	1.62 (0.70–3.72)	0.255
PIV	≤478.3 versus > 478.3	1.86 (0.77–4.51)	0.167
CRP	≤6.6 versus > 6.6	4.54 (1.62–12.7)	0.004
LDH	≤187.5 versus > 187.5	1.01 (0.42–2.42)	0.972
Albumin	≤4.27 versus > 4.27	0.66 (0.27–1.61)	0.368
Age	≤65 versus > 65	1.23 (0.53–2.89)	0.620
HEI	High versus Low	0.94 (0.39–2.22)	0.890
T	1–2 versus 3–4	1.59 (0.69–3.63)	0.269
Stage	I-II versus III-IV	1.26 (0.53–2.99)	0.590
ECOG PS	0–1 versus 2	2.84 (0.92–8.75)	0.068
N	N + versus N0	1.32 (0.53–3.29)	0.549

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune inflammation value, CRP, C-reactive protein; LDH, lactate dehydrogenase; HEI, Hemo-eosinophil inflammation index; ECOG PS, Eastern Cooperative Oncology Group-Performance Status; N, lymphatic metastasis.

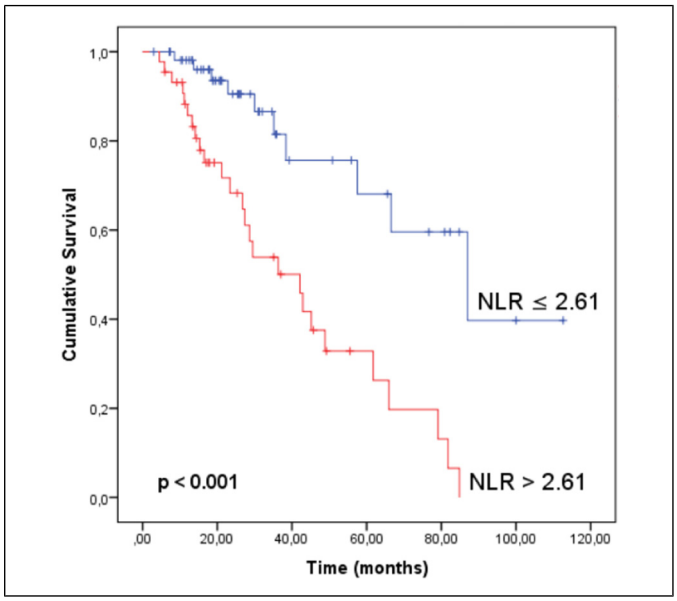


Figure 1. Overall survival according to the Neutrophil-Lymphocyte Ratio (NLR). The P values were calculated using the Log-rank test.

Table 5. Univariate and Multivariate Cox Regression Analysis for the Prediction of Overall Survival.

		Univariate Analysis		Multivariate Analysis	
Variable	Cut-off	HR (%95 Cl)	p	HR (%95 Cl)	p
NLR	≤2.61 versus > 2.61	4.33 (2.02–9.29)	<0.001	6.75 (1.86–24.4)	0.004
PLR	≤133.6 versus > 133.6	2.10 (1.05–4.20)	0.036	1.23 (0.24–6.26)	0.799
MLR	≤0.33 versus > 0.33	2.66 (1.30–5.46)	0.007	0.62 (0.24–1.59)	0.328
SII	≤656.5 versus > 656.5	2.34 (1.17–4.68)	0.015	0.23 (0.03–1.56)	0.133
PIV	≤478.3 versus > 478.3	3.94 (1.89–8.22)	<0.001	3.07 (0.74–12.6)	0.121
CRP	≤6.6 versus > 6.6	3.53 (1.71–7.28)	0.001	2.06 (0.90–4.68)	0.083
LDH	≤187.5 versus > 187.5	0.96 (0.48–1.93)	0.930		
Albumin	≤4.27 versus > 4.27	0.74 (0.37–1.47)	0.402		
Age	≤65 versus > 65	1.35 (0.69–2.67)	0.373		
HEI	High versus Low	0.41 (0.19–0.89)	0.025	1.01 (0.29–3.51)	0.985
T	1–2 versus 3–4	1.74 (0.88–3.41)	0.106		
Stage	I-II versus III-IV	2.68 (1.17–6.13)	0.019	1.36 (0.49–3.80)	0.548
ECOG PS	0–1 versus 2	5.55 (2.52–12.2)	<0.001	3.68 (1.48–9.15)	0.005
N	N + versus N0	0.66 (0.33–1.29)	0.228		

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune inflammation value, CRP, C-reactive protein; LDH, lactate dehydrogenase; HEI, Hemo-eosinophil inflammation index; ECOG PS, Eastern Cooperative Oncology Group -Performance Status; N, lymphatic metastasis.

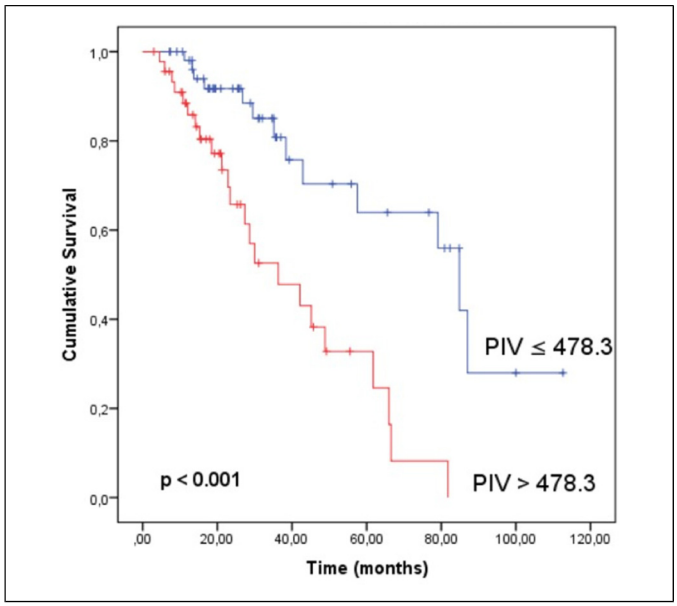


Figure 2. Overall survival according to the Pan-immune Inflammation Value. The P values were calculated using the Log-rank test.

cytokines such as TGF-β and IFN-β, which can cause immunosuppression and facilitate tumor localization and spread.[21]

NLR has been studied to predict PFS and OS in several types of cancer. In a previous meta-analysis, it was found that patients with gastric cancer and elevated NLR values had a 1.45-fold higher frequency of lymph node metastasis. Therefore, using current grading tests in conjunction with the NLR could aid in selecting patients for neoadjuvant treatment.[22] In another study of patients with larynx cancer, an NLR of 4 or higher was found to significantly predict PFS ($p < 0.001$), LRFS ($p < 0.001$), and OS ($p < 0.001$).[23] In another study of patients with larynx cancer, an NLR of 1.85 or higher in blood tests performed before total laryngectomy was identified as a significant negative predictor of LRFS. However, a high NLR level was not found to be a predictor of OS.[24] The results of the current study indicate that NLR >2.61 had a negative impact on PFS and OS in the univariate analysis ($p = 0.07$ and $p < 0.001$, respectively). In the multivariate analysis, NLR was found to have significant predictive value for OS ($p = 0.004$). However, no significant difference was found in NLR values based on lymphatic metastasis status ($p = 0.238$).

Tumor hypoxia causes chemotherapy and radiotherapy resistance. The oxygen-carrying capacity of the blood is reduced due to decreased hemoglobin levels, which is thought to contribute to tumor hypoxia. Gorphe et al found that prechemotherapy anemia and NLR >5 negatively impacted PFS and OS.[25] A study on patients with locally advanced rectal cancer found that both HEI and MLR impacted disease-free survival and OS.[26] Rimini et al also demonstrated that HEI predicted both PFS and OS in univariate and multivariate analyses of patients with anal cancer.[17] In the univariate analysis of the current study, high-risk HEI was found to have a negative impact on OS ($p = 0.025$). In light of these results, the evaluation of HEI, along with parameters such as neutrophils, lymphocytes, platelets, and eosinophils, plays an important role in assessing the prognosis of patients with larynx cancer.

While neutrophils and platelets contribute to tumor development and metastasis, lymphocytes play a key role in anti-tumor responses. High SII values, derived from preoperative peripheral blood tests of bladder cancer patients, have been shown to negatively impact PFS and OS.[27] A meta-analysis has shown that high SII levels predict worse PFS ($p < 0.001$) and OS ($p < 0.001$) in head and neck cancer patients. Furthermore, SII levels have been identified as significant predictors of T stage ($p < 0.001$) and nodal metastasis ($p = 0.002$).[28] In the current study, high SII values similarly demonstrated a negative impact on PFS and OS in the univariate analysis ($p = 0.039$ and $p = 0.015$, respectively).

There have been numerous studies in the literature that have investigated the correlation between various types of cancer and the PIV calculated from the values of neutrophils, platelets, monocytes, and lymphocytes. In a meta-analysis conducted by Guven et al, it was found that the level of PIV had a significant negative impact on OS ($p < 0.001$).[29] Another study also found that OS was negatively affected by preoperative high PIV levels in breast cancer patients.[30] In the univariate analysis of the current study, it was found that PIV greater than 478.3 had a negative impact on PFS and OS ($p = 0.019$ and $p < 0.001$, respectively). Interestingly, a significant difference was observed in PIV values according to lymph node metastasis status ($p = 0.04$). Based on these results, PIV appears to be a significant biomarker for this patient group due to its ability to predict survival and its significant relationship with lymph node metastasis.

Compared to the NLR and PLR, the relationship of the MLR with cancer has been less investigated. In a meta-analysis conducted by Kumarasamy et al, both the NLR and PLR were found to be predictive for OS. Although there were studies showing a significant effect of MLR on OS, it was reported that it could not be routinely used as much as NLR and PLR.[31] In the current study, an MLR value greater than 0.33 was found to have a negative effect on OS ($p = 0.007$), while no effect was observed on PFS ($p = 0.207$). Furthermore, a statistically significant difference was observed between MLR levels ($p = 0.04$) according to lymph node metastasis status.

CRP, which belongs to the family of acute-phase reactants, is a pentameric protein with two forms: pCRP and mCRP. The liver produces pCRP, which can be measured in the bloodstream. mCRP is the active form at the cellular level and plays a crucial role in inflammation by interacting with many cells such as endothelial cells, fibroblasts, and epithelial cells.[32] A study was conducted on patients with cT4b esophageal cancer who had no distant metastasis. The CAR value, obtained by dividing the CRP level by the serum albumin level, had a negative impact on cancer-related survival ($p = 0.029$) and OS ($p = 0.031$).[33] Another study found that patients with gastric cancer who had a CRP level of 3.1 mg/L or higher had a worse prognosis ($p < 0.001$).[34] In the univariate analysis of the current study, CRP levels greater than 6.6 mg/L were

found to have a negative impact on PFS, LRFS, and OS ($p < 0.001$, $p = 0.004$, and $p = 0.001$, respectively). In multivariate analysis, CRP significantly predicted PFS ($p = 0.002$). Additionally, a significant difference in CRP values was observed based on the presence of lymphatic metastasis ($p = 0.03$). Although CRP is commonly used as a biomarker of acute inflammation in clinical practice, these findings suggest that it may also provide insights into chronic inflammation associated with cancer development. Our study suggests that CRP warrants further investigation, as it can predict PFS, LRFS, and OS, and provide insights into lymphatic metastasis.

In addition to serving as a nutritional biomarker, serum albumin is a protein with anti-inflammatory effects. The association with inflammation has prompted the development of new biomarkers by combining serum albumin with other inflammatory markers. Aksoy et al found that low albumin levels (<3.5 g/dL) negatively impacted OS in non-small cell lung cancer patients ($p = 0.001$).[35] Nevertheless, the findings of current study indicate that albumin does not predict PFS, LRFS, and OS in patients with larynx cancer undergoing definitive radiotherapy.

The present study has several limitations. Firstly, it is a retrospective study, and all data were collected from a single centre. Secondly, although patients with conditions that could affect blood parameters were excluded, the results of circulating cell counts may have been influenced by other unknown or undetectable factors, such as medication. Further multicentre or prospective studies are warranted to validate our conclusions.

Conclusion

There has been an increase in research on the relationship between inflammatory biomarkers and cancers. As the use of inflammatory biomarkers is easy, minimally invasive, and low-cost, they have become attractive for use in the cancer prognosis. The current study is the first to comprehensively examine the relationship between larynx cancer and several inflammatory biomarkers, such as NLR, PLR, MLR, SII, PIV, CRP, HEI, albumin, and LDH. Many of these biomarkers have been shown to predict both PFS and OS in patients with larynx cancer undergoing definitive radiotherapy. In this cohort of patients, PIV and CRP emerged as the most noteworthy inflammatory biomarkers, meriting further investigation. As a result of further studies, personalized treatment options may become possible through nomograms created with these inflammatory biomarkers.

Availability of Supporting Data

The datasets generated and/or analyzed during the current study are not publicly available due to privacy but are available from the corresponding author upon reasonable request.

Authors' Contributions

Study concepts and design: T. Koca, RA. Aksoy
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Data analysis and interpretation: T. Koca, AF. Korcum
Statistical analysis: DA. Cetmi, RA. Aksoy
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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

This study received approval from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 595, Date: 02.08.2023). Ethics approval was obtained, but patient consent was not required. The necessity for obtaining informed consent from individual patients was waived by the ethics committee. This waiver was granted because it is an ethics committee-approved retrospective study, all patient information was deidentified, and patient consent was not required.

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