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Prognostic Significance of Dynamic Inflammatory Indices in Head and Neck Cancer During Induction Chemotherapy

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ABSTRACT

Objective: Systemic inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), and hemoglobin-albumin-lymphocyte-platelet score (HALP) have been associated with prognosis in patients with head and neck cancer (HNC). However, the prognostic impact of their dynamic changes during induction chemotherapy has not been well established.

Material and Methods: We retrospectively analyzed 84 patients with histologically confirmed head and neck squamous cell carcinoma who had received induction chemotherapy. Treatment response was evaluated according to RECIST 1.1. Objective response rate (ORR) was defined as the proportion of patients achieving a complete or partial response. Changes in NLR, PLR, LMR, neutrophil-to-monocyte ratio (NMR), SII, and HALP score between baseline and post-induction were categorized as increased or not increased. Logistic regression was used to assess associations with ORR, whereas Cox regression was used to evaluate progression-free survival (PFS) and overall survival (OS).

Results: The median follow-up was 16.7 months. The ORR was 77.4%; 7 patients achieved a complete response, 58 achieved a partial response, 17 had stable disease, and 2 had progressive disease. Multivariate analysis demonstrated that increased NLR was independently associated with a lower ORR [odds ratio: 0.24, 95% confidence interval (CI): 0.08-0.75, p=0.014]. For survival outcomes, increased NLR [hazard ratio (HR): 0.13, 95% CI: 0.04-0.43, p<0.001) and decreased LMR (HR: 0.27, 95% CI: 0.09-0.83, p=0.022) predicted longer PFS. Increased NLR showed a borderline association with OS (HR=0.29; 95% CI: 0.08-1.00; p=0.050). Other indices, including PLR, NMR, SII, and HALP, were not statistically significant.

Conclusion: Dynamic changes, particularly in NLR and LMR during induction chemotherapy, are independent prognostic factors for PFS in HNC. These findings support incorporating longitudinal monitoring of inflammatory indices into routine clinical practice.

Keywords: Head and neck cancer; induction chemotherapy; inflammatory markers; neutrophil-to-lymphocyte ratio; prognostic index; survival

INTRODUCTION

Head and neck cancer (HNC) comprises a diverse group of malignancies originating from the nasopharynx, larynx, oropharynx, hypopharynx, oral cavity, salivary glands, and paranasal sinuses, and represents a significant global health burden.[1] Management strategies for HNC vary according to the tumor stage and the anatomical site of the disease. While early-stage disease is typically managed with surgery or radiotherapy, induction chemotherapy is generally reserved for selected patients with locally advanced tumors.

Recent research has emphasized identifying prognostic factors that help clinicians recognize patients with HNC who

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are at higher risk of recurrence and mortality.[2] Established prognostic indicators include TNM stage, presence of extranodal extension, human papilloma virus (HPV) status, and patient-related variables such as age, functional performance, and history of tobacco and alcohol use.[3-5]

Head and neck squamous cell carcinoma (HNSCC) represents a group of biologically diverse tumors characterized by variable clinical behavior and heterogeneous responses to treatment. Despite advances in surgery, radiation, and systemic therapy, the prognosis for advanced-stage disease remains suboptimal. Induction chemotherapy is often employed in patients with locally advanced or unresectable tumors to achieve tumor shrinkage and facilitate subsequent definitive therapy.[6]

Recent evidence underscores the pivotal role of systemic inflammation in tumor progression, treatment resistance, and overall prognosis in malignancies, including HNSCC. Routinely available blood measures, such as, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been suggested as useful biomarkers for predicting patient outcomes. Elevated pre-treatment NLR has been consistently associated with poorer overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) in HNSCC; multiple meta-analyses have reported hazard ratios (HRs) for OS and DFS ranging from approximately 1.5 to 1.9.[7,8]

For instance, a pooled analysis involving over 6,800 patients found that high NLR predicted worse OS (HR=1.68), DFS (HR=1.76), PFS (HR=1.53), and cancer-specific survival (HR=1.45).[9]

While the prognostic value of baseline inflammatory scores is well documented, few studies have investigated how these markers change in response to induction chemotherapy and whether such changes carry prognostic significance in head and neck cancer.[10,11]

The prognostic value of systemic inflammatory indices in head and neck cancers has been extensively investigated in previous studies.[12] However, most of the existing literature has focused solely on baseline values, with limited attention given to changes in these parameters during treatment. Our study addresses this gap by evaluating the impact of relative changes in inflammatory indices before and after induction chemotherapy on survival outcomes. This approach not only considers initial measurements but also captures the biological response to treatment, potentially providing a more accurate prognosis.

The aim of this study was to evaluate the predictive and prognostic value of inflammatory indices measured before and after induction chemotherapy in patients with HNC and to explore whether dynamic changes in these markers are associated with survival outcomes.

MATERIAL AND METHODS

Study Design and Patient Population

This retrospective cohort study included patients with histologically confirmed HNSCC who received induction chemotherapy followed by definitive local treatment at the Medical Oncology Department of University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital between June 2016 and May 2021. Eligible patients met the following criteria:

- Age ≥18 years;
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2;
- Availability of baseline and post-induction laboratory and imaging data;
- No prior systemic therapy for the index malignancy;
- Adequate organ function as per institutional laboratory reference ranges;
- Follow-up data of at least 3 months.

Patients with concomitant malignancies, uncontrolled infections, incomplete follow-up data, or those lost to follow-up within the first month after initiation of treatment were excluded.

Data Collection and Variables

Clinical, pathological, and laboratory data were extracted from the institutional electronic medical records. Variables included age, sex, ECOG PS, and comorbidities. Tumor characteristics included primary tumor site, stage according to the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system, and histological grade. Laboratory parameters included neutrophil, lymphocyte, monocyte, and platelet counts, hemoglobin concentration, serum albumin, and total protein levels, all of which were obtained within one week before initiation of induction chemotherapy and again within one month after its completion.

From these laboratory parameters, the following inflammatory and nutritional indices were calculated both pre- and post-induction chemotherapy.

Clinical Staging

All patients were staged according to the 8th edition of the AJCC staging system. Clinical staging was performed using the TNM classification, which incorporates the parameters T (tumor size and local extension), N (regional lymph node involvement), and M (presence of distant metastasis).[13]

According to the AJCC 8th edition, clinical stages for head and neck cancers were grouped as follows:

• Stage III: T3 N0 M0 or any T, N1 M0

• Stage IVA: T4a N0-N2 M0 or any T, N2 M0

• Stage IVB: Any T, N3 M0 or T4b any N, M0

Site-specific TNM definitions for the primary tumor (larynx, nasopharynx, oropharynx, hypopharynx, oral cavity, etc.) were assigned according to AJCC 8th edition criteria. For HPV-associated oropharyngeal carcinomas, p16 immunohistochemical staining status was assessed, and the AJCC 8th edition staging system for p16-positive tumors was applied.

TNM parameters were determined based on radiological imaging at the time of diagnosis, endoscopic examination findings, and histopathological reports.

Inflammatory Index Calculation

Inflammatory and nutritional indices were calculated for each patient using baseline hematological parameters obtained prior to treatment initiation. The following formulas were applied:

• NLR: neutrophil count ($\times10^9$/L) ÷ lymphocyte count ($\times10^9$/L)

• PLR: platelet count ($\times10^9$/L) ÷ lymphocyte count ($\times10^9$/L)

• LMR: lymphocyte count ($\times10^9$/L) ÷ monocyte count ($\times10^9$/L)

• Neutrophil-to-monocyte ratio (NMR): neutrophil count ($\times10^9$/L) ÷ monocyte count ($\times10^9$/L)

• Systemic immune-inflammation index (SII): (platelet count × neutrophil count) ÷ lymphocyte count

• Hemoglobin, albumin, lymphocyte, and platelet score (HALP): hemoglobin (g/L) × albumin (g/L) × lymphocyte count ($\times10^9$/L) ÷ platelet count ($\times10^9$/L)

This formula expresses the percentage change in each inflammatory index from baseline (pre-induction) to post-induction measurement. Percentage changes from baseline to post-treatment were calculated for each index.

Association Between Pre-Post Induction Changes and Outcomes

Inflammatory indices (NLR, PLR, NMR, SII, LMR, HALP) were recorded before and after induction chemotherapy. The change in each inflammatory index was calculated as the percentage change: $\%\Delta=100 \times (\text{post-pre})/\text{pre}$. A decrease in NLR/PLR/NMR/SII and an increase in LMR/HALP were considered "Increased." For clinical interpretability, patients were categorized as "Increased" (≥10% change) or "Not Increased" ($|\%\Delta|<10\%$). We selected a 10% threshold pragmatically, as no standardized cut-off exists in the literature. This approach was intended to provide consistency across indices and to facilitate clinical interpretability, although validation in larger prospective cohorts will be necessary.

Clinical Outcomes

The primary endpoint was PFS, defined as the interval from initiation of induction chemotherapy to radiologically confirmed disease progression or death from any cause, whichever occurred first. The secondary endpoints were OS and objective response rate (ORR).

OS was defined as the time from initiation of induction chemotherapy to death from any cause. Patients who were alive at the time of last follow-up were censored at the date last known to be alive.

ORR was defined as the proportion of patients whose best overall response was either a complete response (CR) or a partial response (PR), evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[9-15]

Tumor response assessment was performed using contrast-enhanced computed tomography and/or magnetic resonance imaging of the primary tumor and metastatic sites at baseline, after completion of induction chemotherapy, and subsequently every 8-12 weeks or as clinically indicated.

Per RECIST 1.1 Definitions

CR: Disappearance of all target lesions, with all pathological lymph nodes reduced to <10 mm in short axis.

PR: A decrease of at least 30% in the sum of the diameters of target lesions, relative to the baseline sum of the diameters. Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum diameters recorded as reference. Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions (minimum absolute increase of 5 mm), or appearance of one or more new lesions.

All imaging studies were independently reviewed by two experienced board-certified radiologists who were patients' blinded to patients' clinical and laboratory data. Discrepancies were resolved by consensus in a joint review meeting. Non-target lesions were evaluated according to RECIST qualitative criteria and included in the determination of progression.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Statistical Analysis

Continuous variables were reported as median values with interquartile ranges or as means with standard deviations,

depending on their distribution, and were compared using either the Student's t-test or the Mann-Whitney U test. Categorical variables were summarized as frequencies (percentages) and compared using the chi-square test or Fisher's exact test, as appropriate.

Kaplan-Meier survival curves were constructed for PFS and OS, and differences between groups were compared using the log-rank test. The median follow-up time was calculated using the reverse Kaplan-Meier method.

Univariate and multivariate analyses were performed to assess the association between changes in inflammatory indices and outcomes. Logistic regression was used for ORR, and Cox proportional hazards regression for PFS and OS. Variables with $p<0.10$ in univariate analyses were entered into multivariate models. The proportional hazards assumption was tested using Schoenfeld residuals.

All statistical analyses were conducted using SPSS version 30 (IBM Corp., Armonk, NY, USA) and BlueSkyStatistics software version 10.3.2. A two-sided p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval no: 84/11, date: 16.03.2020). Given the retrospective nature of the study, informed consent was waived in accordance with institutional policy and national regulations. All procedures were conducted in compliance with the Declaration of Helsinki (2013 revision).

RESULTS

In this study cohort, 83.4% of the patients were male and 16.6% were female, with a median age of 58.2 years (range: 30-82 years). More than half of the patients (54.7%) were younger than 60 years of age. The majority (80.9%) were current smokers, and 60.7% had ECOG PS 0, indicating good baseline functional capacity. Comorbidities were present in 44.1% of the population.

The most common primary tumor site was the nasopharynx (36.9%), followed by the larynx (29.7%). Most patients presented with advanced-stage disease, with stage IVA comprising 66.6% of cases. HPV status was not assessed for the majority (91.7%). Induction chemotherapy was primarily based on docetaxel-cisplatin-5-fluorouracil (DCF) (75.0%). Treatment responses included PR in 69.0% of patients, CR in 8.4%, SD in 20.2%, and PD in 2.4% (Table 1). After induction chemotherapy, most patients (91.6%) proceeded to concurrent chemoradiotherapy, primarily with cisplatin (79.7%). Disease progression was observed in 23.8% of patients, while 76.2% remained progression-free during a median follow-up of 16.7 months. Median PFS and OS were not reached. Overall, the results emphasize the predominant use of DCF-based induction therapy and the high rate of disease control achieved following indoction chemotherapy and chemoradiotherapy (Table 2).

The median pre-induction values of the inflammatory indices were as follows: NLR, 2.64; PLR, 145.35; LMR, 2.97; NMR, 8.20; SII, 786.93; and HALP score, 4.460. Following induction

TABLE 1: Clinical and demographical parameters.

Sex n (%)	
Male	70 (83.4)
Female	14 (16.6)
Age (years)	
Median (minimum-maximum)	58.2 (30-82)
Age groups n (%)	
<60 years	46 (54.7)
≥60 years	38 (45.3)
Smoking n (%)	
Current smoker	68 (80.9)
Never smoke	16 (19.1)
ECOG PS n (%)	
0	51 (60.7)
1	30 (35.7)
2≤	3 (3.6)
Comorbidity n (%)	
Yes	37 (44.1)
No	47 (55.9)
Primer n (%)	
Nasopharynx	31 (36.9)
Larynx	25 (29.7)
Oral cavity	8 (9.5)
Oropharynx	9 (10.7)
Hypopharynx	7 (8.3)
Paranasal sinuses	4 (4.7)
Stage n (%)	
III	7 (8.3)
IVA	56 (66.6)
IVB	21 (25.0)
HPV status n (%)	
Not evaluated	77 (91.7)
Positive	6 (7.1)
Negative	1 (1.2)

HPV: Human papillomavirus; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

chemotherapy, the median values were: NLR 2.37, PLR 152.88, LMR 3.13, NMR 8.00, SII 617.13, and HALP 3.53. Relative percentage changes (%Δ) indicated notable decreases in NLR (-9.96%), SII (-10.54%), and, particularly, HALP (-21.47%), whereas increases were observed in PLR (+8.89%), LMR (+9.58%), and NMR (+17.76%).

TABLE 2: Treatment parameters and survival.

Induction CT (ICT)	
DCF	63 (75.0)
Cisplatin-gemcitabine	15 (17.8)
DC	6 (7.2)
Treatment response (TR)	
CR	7 (8.4)
PR	58 (69.0)
SD	17 (20.2)
PD	2 (2.4)
CRT (after ICT)	
Yes	77 (91.6)
No	7 (8.4)
CRT with	
Cisplatin	67 (79.7)
Carboplatin	2 (2.4)
Cetuximab	7 (8.4)
Carboplatin+paclitaxel	2 (2.4)
Progression	
Yes	20 (23.8)
No	64 (76.2)
Median PFS (months)	NR
Exitus	
Yes	14 (16.7)
No	70 (83.3)
Median OS (months)	NR
Median follow-up (months)	16.7

CT: Chemotherapy; DC: Docetaxel-cisplatin; DCF: Docetaxel-cisplatin-5FU; CRT: Chemoradiotherapy; PSF: Progression-free survival; OS: Overall survival; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NR: Not reached.

These trends suggest that systemic inflammatory and nutritional markers undergo dynamic modulation during induction chemotherapy, potentially reflecting treatment response and tumor-host interactions (Table 3).

When patients were stratified according to changes in inflammatory indices before and after induction chemotherapy, a significant association was observed between NLR dynamics and treatment response (p=0.035). Patients with increased NLR after induction showed a higher proportion of PD (76.5%) than patients without an increase (23.5%).

Similarly, changes in SII were significantly correlated with response rates (p=0.043); increased SII was associated with a higher frequency of PD (23.5%), whereas the non-increase group showed a complete absence of stable disease. In contrast, variations in PLR, LMR, NMR, and HALP did not demonstrate statistically significant relationships with treatment response (all p>0.05). These findings highlight that unfavorable shifts in systemic inflammatory markers, particularly NLR and SII, may reflect poor tumor control following induction therapy (Table 4).

Analysis of survival outcomes, based on changes in inflammatory indices before and after induction chemotherapy, demonstrated that only variation in NLR had a statistically significant effect on PFS. Patients with increased NLR exhibited a shorter median PFS [21.6 months; 95% confidence interval (CI): 16.6- not reached (NR)] compared with patients without an increase, whose median PFS was not reached (p=0.009, log-rank test). No significant association between NLR changes and OS) was observed (p=0.25).

Changes in PLR, LMR, NMR, SII, and HALP did not show statistically significant associations with either PFS or OS (all p>0.05). These findings suggest that among the evaluated indices, dynamic changes in NLR may serve as a prognostic marker for disease progression, whereas other inflammatory parameters do not demonstrate predictive value in this cohort (Table 5).

TABLE 3: Median values and percentage changes of inflammatory indices before and after induction chemotherapy.

	Pre-induction		Post-induction		median
Variable	**Median (cut-off)**	**IQR**	**Median (cut-off)**	**IQR**	**%Δ**
NLR	2.64	2.16-3.86	2.37	1.50-3.25	-9.96
PLR	145.35	115.20-191.91	152.88	106.11-205.02	8.89
LMR	2.97	2.25-3.68	3.13	2.23-4.89	9.58
NMR	8.20	6.21-10.12	8.00	5.34-11.36	17.76
SII	786.93	565.30-1149.71	617.13	359.15-947.70	-10.54
HALP	4.460	2.75-5.63	3.53	2.63-4.87	-21.47

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; IQR: Interquartile range.

TABLE 4. Treatment response rates according to pre–post induction chemotherapy changes in inflammatory indices.

Index	Group	n (%)	CR	SD	PD	p-value
NLR	Increased	3 (42.9%)	24 (41.4%)	13 (76.5%)	2 (100.0%)	0.035
	Not increased	4 (57.1%)	34 (58.6%)	4 (23.5%)	0 (0.0%)	
PLR	Increased	3 (42.9%)	27 (46.6%)	7 (41.2%)	2 (100.0%)	0.469
	Not increased	4 (57.1%)	31 (53.4%)	10 (58.8%)	0 (0.0%)	
LMR	Increased	3 (42.9%)	26 (44.8%)	11 (64.7%)	1 (50.0%)	0.534
	Not increased	4 (57.1%)	32 (55.2%)	6 (35.3%)	1 (50.0%)	
NMR	Increased	7 (100.0%)	51 (87.9%)	14 (82.4%)	2 (100.0%)	0.625
	Not increased	0 (0.0%)	7 (12.1%)	3 (17.6%)	0 (0.0%)	
SII	Increased	5 (71.4%)	21 (36.2%)	4 (23.5%)	2 (100.0%)	**0.043**
	Not increased	2 (28.6%)	37 (63.8%)	13 (76.5%)	0 (0.0%)	
HALP	Increased	2 (28.6%)	18 (31.0%)	5 (29.4%)	0 (0.0%)	0.826
	Not increased	5 (71.4%)	40 (69.0%)	12 (70.6%)	2 (100.0%)	

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CR: Complete response; SD: Stable disease; PD: Progressive disease.

TABLE 5. Progression-free survival and overall survival according to pre-post induction chemotherapy changes in inflammatory indices.

Index	Change group	Median PFS (mo) (95% CI)	p (log-rank)	Median OS (mo) (95% CI)	p (log-rank)
NLR	Increased	21.6 (16.6-NR)	0.009	NR (26.7-NR)	0.25
	Not Increased	NR		NR (58.4-NR)	
PLR	Increased	NR (18.0-NR)	0.974	NR (40.8-NR)	0.923
	Not Increased	NR (21.6-NR)		NR (58.4-NR)	
LMR	Increased	18.6 (17.1-NR)	0.064	58.4 (22.9-NR)	0.115
	Not Increased	NR		NR (40.8-NR)	
NMR	Increased	NR (21.6-NR)	0.923	NR (58.4-NR)	0.519
	Not Increased	28.0 (18.0-NR)		40.8 (NR-NR)	
SII	Increased	NR (21.6-NR)	0.520	NR	0.258
	Not Increased	NR (18.0-NR)		58.4 (50.8-NR)	
HALP	Increased	NR (18.6-NR)	0.508	58.4 (58.4-NR)	0.873
	Not Increased	NR (21.6-NR)		NR (40.8-NR)	

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CI: Confidence interval; OS: Overall survival; NR: Not reached.

The Kaplan-Meier curve demonstrates a clear separation in PFS between patients with increased NLR after induction chemotherapy (blue line) and those without an increase (red line). Patients in the "increased" group experienced earlier disease progression, with a significantly shorter median PFS (21.6 months) compared to the "non-increased" group, whose median PFS was not reached during follow-up (log-rank p=0.0093) (Figure 1).

In the analysis of OS according to changes in the NLR after induction chemotherapy, patients with increased NLR had a numerically shorter OS than those without an increase; this difference did not reach statistical significance (log-rank p=0.25). The median OS was NR in either group, and the 95% CIs were wide, reflecting the limited number of deaths during follow-up. Kaplan–Meier estimates showed a trend toward better long-term survival in the non-increased NLR group, with the survival curves beginning to diverge after approximately 20 months of follow-up (Figure 2).

For LMR, a post-treatment increase was also significantly associated with shorter PFS (HR=0.27, 95% CI=0.09-0.83, p=0.022), but was not significantly associated with OS or ORR. In contrast, post-treatment changes in PLR, NMR, SII, and HALP did not show statistically significant associations with ORR, PFS, or OS in the multivariate models. These findings highlight the prognostic relevance of NLR and, to a lesser extent, LMR dynamics in predicting clinical outcomes (Table 6).

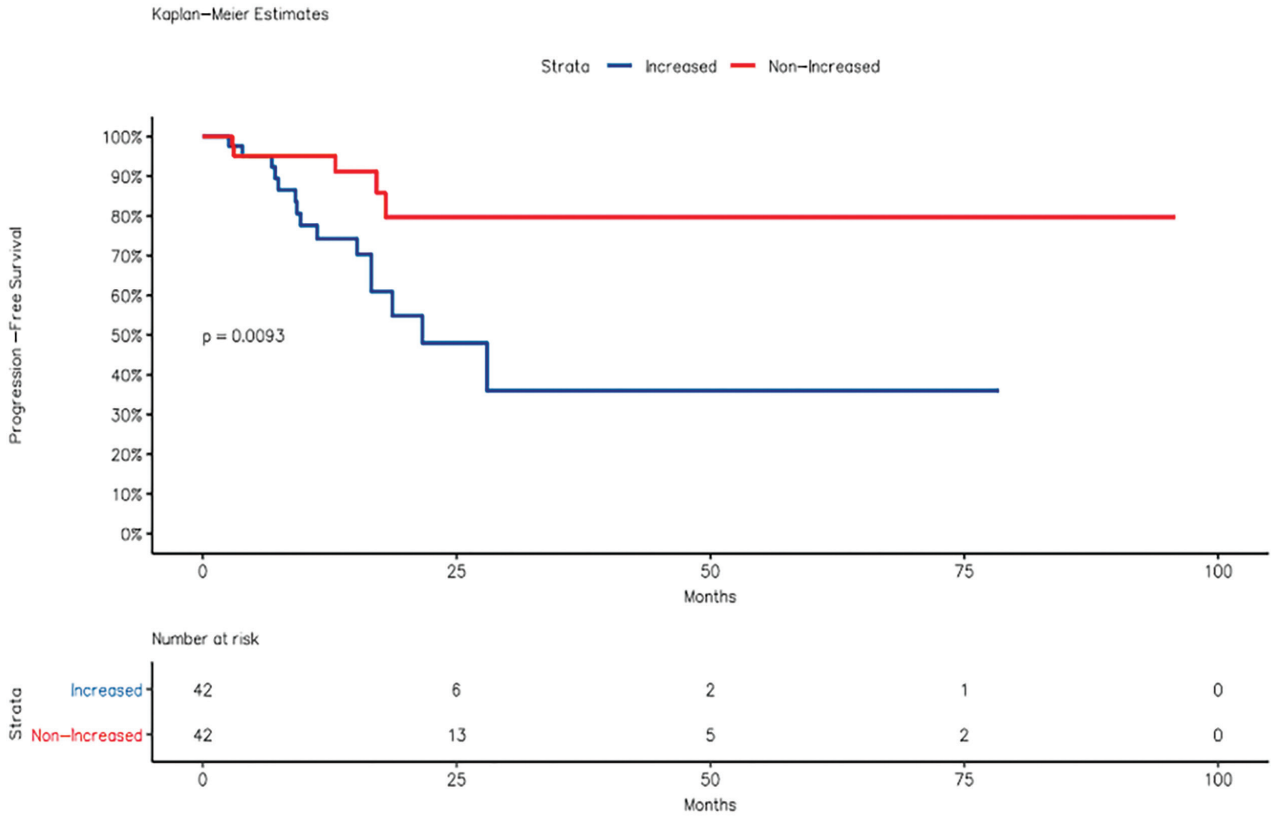

FIGURE 1: Kaplan-Meier curves for progression-free survival (PFS) according to pre-post NLR change status. Patients with increased NLR after induction chemotherapy (blue line) showed significantly shorter PFS compared with those without an increase in NLR (red line) (median PFS: 21.6 months vs. not reached; log-rank p=0.009). Numbers at risk are provided below the x-axis.

NLR: Neutrophil-to-lymphocyte ratio.

DISCUSSION

In this study, we demonstrated that dynamic changes in systemic inflammatory indices, particularly NLR and LMR, during induction chemotherapy are significantly associated with treatment response and PFS in patients with HNSCC. Specifically, increased NLR and decreased LMR after induction therapy independently predicted poorer PFS, while increased NLR was also associated with a lower ORR and had a borderline association with poorer overall survival. These findings highlight the potential role of longitudinal monitoring of inflammatory biomarkers as a complementary prognostic tool in this patient population.

The prognostic significance of baseline inflammatory indices, such as NLR, PLR, LMR, SII, and HALP, has been reported in multiple malignancies, including HNSCC.[16-21] Elevated baseline NLR has been consistently associated with adverse outcomes, reflecting a systemic, tumor-promoting inflammatory state characterized by neutrophil-mediated suppression of cytotoxic lymphocytes and enhanced tumor angiogenesis.[22] Conversely, higher LMR has been associated with improved clinical outcomes, a relationship that likely reflects preserved lymphocyte-mediated antitumor immunity and diminished monocyte-driven pathways of tumor progression.[23] These results demonstrate that temporal changes in inflammatory indices during systemic treatment provide prognostic value beyond that of baseline blood parameters alone. They also enhance existing evidence by potentially capturing early biological implications of host-tumor-treatment interactions.

Notably, unlike NLR and LMR, no significant prognostic associations were observed for SII and HALP in our cohort. Previous studies have demonstrated the prognostic importance of these indices in head and neck cancers and other solid tumors, generally reporting that high SII and low HALP levels are associated with poorer survival outcomes.[19,24] The failure to detect this association in our study may be explained by the relatively small sample size, heterogeneity in primary tumor sites, and differences in treatment regimens. Furthermore, it is possible that NLR and LMR, which directly reflect lymphocyte-monocyte and neutrophil-lymphocyte

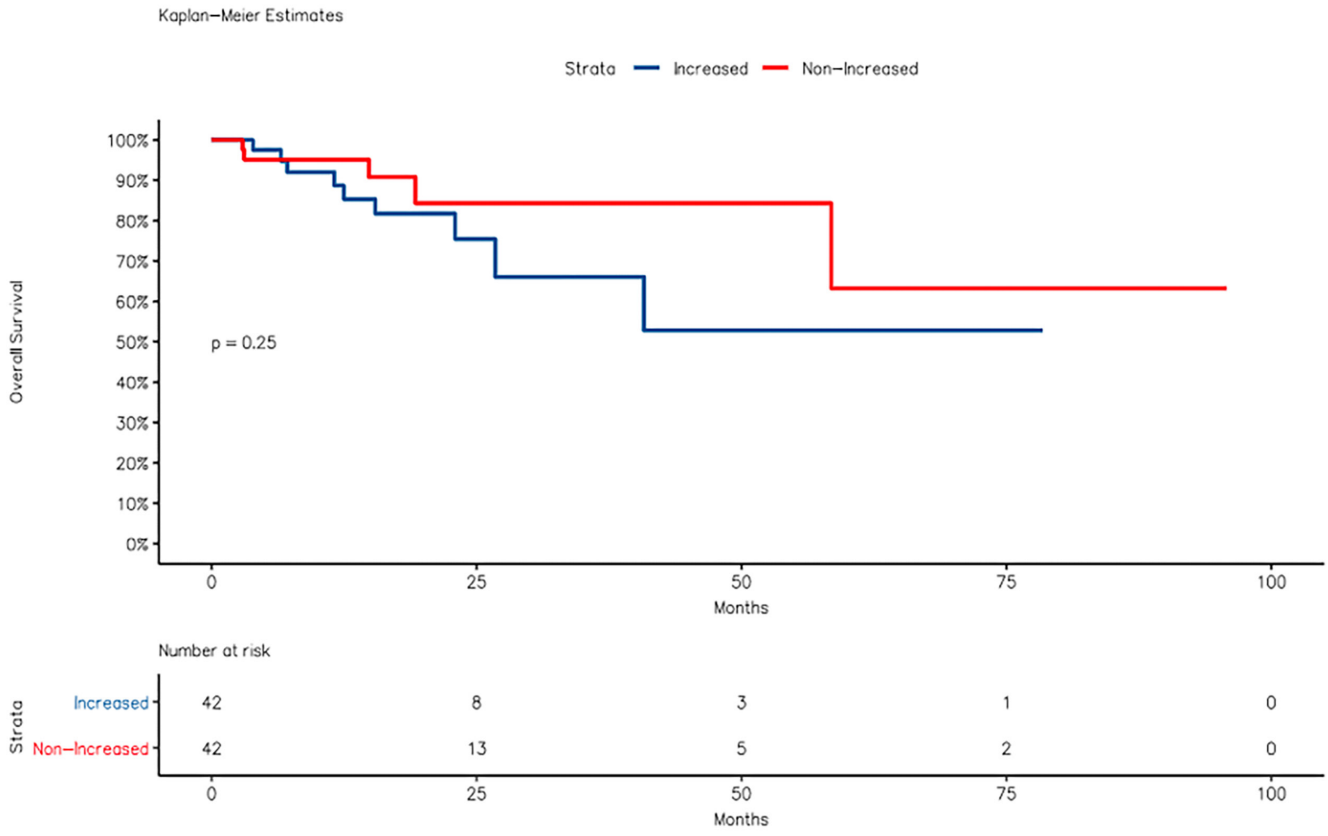

FIGURE 2: Kaplan-Meier curves for overall survival according to pre-post NLR change status.

Multivariate analyses demonstrated that an increase in NLR after induction chemotherapy was independently associated with significantly lower odds of achieving an objective response (OR=0.24, 95% CI=0.08-0.75, p=0.014) and with a markedly shorter progression-free survival (HR=0.13, 95% CI=0.04-0.43, p<0.001). Although a similar trend was observed for overall survival (HR=0.29, 95% CI=0.08-1.00), the association was borderline significant (p=0.05).

CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; NLR: Neutrophil-to-lymphocyte ratio.

interactions, may be more sensitive indicators of host-tumor immune dynamics during induction chemotherapy than composite indices such as SII and HALP. Larger prospective studies are needed to clarify these differences.

Neutrophils and monocytes exert tumor-promoting effects through distinct but complementary mechanisms. Neutrophils facilitate tumor progression and immunosuppression by secreting pro-angiogenic factors such as vascular endothelial growth factor and matrix metalloproteinase-9 and by suppressing T-cell activity through arginase-1-mediated arginine depletion.[25] On the other hand, monocytes attracted to the tumor microenvironment can differentiate into tumor-associated macrophages; these cells promote angiogenesis, immune evasion, extracellular matrix remodeling, and metastasis formation.[26] Therefore, increasing NLR or decreasing LMR during treatment may reflect persistent tumor-promoting inflammation and an immunosuppressive microenvironment, which is indicative of more aggressive disease biology or inadequate systemic immune recovery.

From a clinical perspective, identifying patients at high risk of progression using simple, inexpensive, and readily available hematologic parameters could allow for more effective optimization of treatment strategies. For example, patients with unfavorable changes in NLR or LMR may benefit from more frequent follow-up, early intensification of therapy, or inclusion in clinical trials evaluating new treatment strategies such as immunotherapy or anti-inflammatory approaches.

Study Limitations

Our study has several strengths, including the dynamic assessment of treatment-related biomarker changes, multivariate adjustment for potential confounders, and the inclusion of multiple inflammatory indices for comparative purposes. However, several limitations should be considered. The retrospective design and single-center nature of the study may limit the generalizability of the findings. While the sample size was sufficient for multivariate analysis, it may have limited the power to detect smaller effects, particularly in

TABLE 6: Multivariate logistic and Cox regression analyses for the association between pre–post changes in inflammatory indices and outcomes.

Index	Outcome	Group	OR/HR (95% CI)	p-value
NLR	ORR (logistic)	Increased vs. not increased	0.24 (0.08-0.75)	**0.014**
NLR	PFS	Increased vs. not increased	0.13 (0.04-0.43)	**<0.001**
NLR	OS	Increased vs. not increased	0.29 (0.08-1.00)	**0.050**
PLR	ORR (logistic)	Increased vs. not increased	1.08 (0.39-2.96)	0.883
PLR	PFS	Increased vs. not increased	0.91 (0.29-2.82)	0.876
PLR	OS	Increased vs. not increased	0.45 (0.10-2.03)	0.300
LMR	ORR (logistic)	Increased vs. not increased	0.55 (0.20-1.53)	0.255
LMR	PFS	Increased vs. not increased	0.27 (0.09-0.83)	**0.022**
LMR	OS	Increased vs. not increased	0.49 (0.14-1.75)	0.277
NMR	ORR (logistic)	Increased vs. not increased	1.44 (0.33-6.17)	0.626
NMR	PFS	Increased vs. not increased	1.03 (0.23-4.61)	0.964
NMR	OS	Increased vs. not increased	0.35 (0.03-3.55)	0.379
SII	ORR (logistic)	Increased vs. not increased	1.60 (0.54-4.69)	0.395
SII	PFS	Increased vs. not increased	2.07 (0.57-7.44)	0.263
SII	OS	Increased vs. not increased	4.24 (0.80-22.49)	0.089
HALP	ORR (logistic)	Increased vs. not increased	1.36 (0.44-4.27)	0.594
HALP	PFS	Increased vs. not increased	1.51 (0.44-5.16)	0.506
HALP	OS	Increased vs. not increased	0.86 (0.20-3.72)	0.854

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; OS: Overall survival; ORR: Objective response rate; PFS: Progression-free survival.

terms of OS. Indeed, the low number of events, particularly for overall survival, further reduces the robustness of our results. Therefore, the findings should be considered exploratory and hypothesis-generating.

Additionally, potential confounding factors that could affect inflammatory indices, such as intercurrent infections or corticosteroid use, were not evaluated. Another important limitation is that HPV status, which is well-known for its prognostic significance in oropharyngeal carcinoma, was not determined in the vast majority of patients. This omission may have introduced residual confounding and may have reduced the interpretability of the results for HPV-related subgroups.

CONCLUSION

In conclusion, dynamic changes in inflammatory indices, particularly NLR and LMR, during induction chemotherapy provide independent prognostic information in patients with HNSCC. These simple, cost-effective biomarkers may aid in risk stratification and guide treatment decisions. From a clinical perspective, patients exhibiting unfavorable changes in NLR or LMR during induction chemotherapy may warrant closer surveillance, earlier treatment intensification, or prioritization for clinical trial enrollment. Prospective multicenter studies are warranted to validate these findings and to explore whether integrating inflammatory indices into treatment algorithms can improve patient outcomes.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval no: 84/11, date: 16.03.2020).

Informed Consent: Informed consent was waived in accordance with institutional policy and national regulations.

Footnotes

Authorship Contributions

Concept: E.Z., G.İ.İ., D.Y., A.K., E.E.K., Design: E.Z., G.İ.İ., M.C.A., D.Y., A.K., E.E.K., Data Collection or Processing: E.Z., İ.D., M.C.A., Ö.B., Analysis or Interpretation: E.Z., İ.D., A.K., Literature Search: E.Z., G.İ.İ., D.Y., Ö.B., Writing: E.Z., E.E.K.

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