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Pretreatment Neutrophil-to-Lymphocyte Ratio as an Independent Prognostic Biomarker in Esophageal Cancer Following Neoadjuvant Chemoradiotherapy

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ABSTRACT

Background: *The neutrophil-to-lymphocyte ratio (NLR) has emerged as a promising systemic inflammatory biomarker with potential prognostic value across various solid tumors. However, its prognostic significance in patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy (nCRT) remains inconsistent. This study aimed to investigate the independent prognostic value of pretreatment NLR in patients with esophageal cancer treated with nCRT.*

Methods: *This retrospective cohort study included 72 patients with stage II–IVA esophageal cancer who received nCRT between July 2020 and December 2023. Pretreatment NLR was calculated from complete blood count measurements obtained within one week before treatment initiation. The optimal NLR cutoff value was determined using maximally selected rank statistics. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan–Meier method and Cox proportional hazards regression analyses.*

Results: *The optimal pretreatment NLR cutoff was identified as 2.4 for both OS and PFS. Patients with an NLR >2.4 had significantly poorer PFS (p=0.013) and OS (p<0.001) than those with an NLR ≤2.4. In multivariable Cox regression analysis, pretreatment NLR >2.4 remained independently associated with worse PFS (HR=2.18, 95% CI: 1.09–4.37, p=0.028) and OS (HR=2.23, 95% CI: 1.11–4.49, p=0.024). In addition, poor response to nCRT was independently associated with inferior survival outcomes, whereas pretreatment NLR was not significantly associated with treatment response.*

Conclusions: *Elevated pretreatment NLR was independently associated with poorer survival outcomes in patients with esophageal cancer treated with neoadjuvant chemoradiotherapy. Given the exploratory nature of the findings and the methodological limitations of the study, external validation using NLR as a continuous variable in adequately powered prospective cohorts is required before clinical implementation.*

Keywords: *Esophageal cancer; Neutrophil-to-lymphocyte ratio; Neoadjuvant chemoradiotherapy; Prognosis; Survival*

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1. INTRODUCTION

Esophageal cancer (EC) is recognized as one of the most common and lethal malignancies worldwide, accounting for an estimated 511,054 new cases and 445,391 deaths according to 2022 data (1). This malignancy exhibits high incidence rates, particularly in regions such as Eastern Asia and Eastern Africa, and occurs significantly more frequently in males than in females (1, 2). Globally, it ranks seventh among the leading causes of cancer-related mortality (1). EC comprises two predominant histo pathological subtypes: esophageal squamous cell carcinoma (ESCC), which is primarily prevalent in Eastern countries and strongly associated with risk factors such as tobacco and alcohol consumption (3); and adenocarcinoma (AC), which is more common in Western countries and linked to etiological factors including gastroesophageal reflux disease (GERD), Barrett's esophagus, and obesity (4, 5). Despite advances in diagnostic and therapeutic modalities, the prognosis of EC remains poor; according to recent SEER data, the five-year survival rate is 22.2% (6). Although Tumor-Node-Metastasis (TNM) staging is the primary determinant of prognosis, the heterogeneity in survival outcomes among patients within the same stage necessitates the investigation of additional prognostic factors (7).

In recent years, an increasing number of studies have focused on the role of systemic inflammation in cancer development and progression. Cancer-related inflammation triggers DNA damage, thereby promoting angiogenesis, enhancing cellular proliferation, and facilitating tumor invasion and metastasis (8-11). Hematological markers utilized in the assessment of systemic inflammation have been associated with poor prognosis in various malignancies; notable among these are the Glasgow Prognostic Score (GPS), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and neutrophil-to-lymphocyte ratio (NLR) (12, 13). NLR is a simple parameter derived by dividing the absolute neutrophil count by the absolute lymphocyte count, and it has been demonstrated to hold prognostic value in solid tumors (14). However, despite accumulating evidence supporting the prognostic value of NLR, inconsistencies remain across individual studies, particularly with respect to different tumor types and clinical settings (14–16). These discrepancies may stem from variations in study designs, sample sizes, and therapeutic strategies. Although broad meta-analyses (14,17) have established the general prognostic value of systemic inflammatory markers across solid tumors, more recent studies have increasingly focused on disease-specific settings, such as patients with esophageal cancer receiving neoadjuvant chemoradiotherapy.

Recent studies have increasingly evaluated the prognostic role of NLR in patients with esophageal cancer receiving nCRT. However,

considerations, the present study aimed to evaluate the independent prognostic value of pre-treatment NLR on survival outcomes in a well-defined cohort of esophageal cancer patients receiving nCRT.

2. MATERIALS AND METHODS

2.1. Study Design

This study was designed as a retrospective cohort analysis to evaluate the relationship between the NLR and prognostic outcomes in esophageal cancer patients who received neo adjuvant chemo radiotherapy (nCRT). The research encompasses 72 patients diagnosed with esophageal cancer at our institution between July 2020 and December 2023, who underwent nCRT following a multidisciplinary tumor board decision. Patients' demographic characteristics, treatment courses, and follow-up data were retrospectively collected from medical records.

2.2. Relationship with Previous Publication

The patient cohort in this study consists of the same population reported in our previous publication (18). That study focused on the impact of treatment response on survival outcomes; systemic inflammatory markers were neither examined nor included in that analysis. The current study is based on a distinct hypothesis and evaluates the prognostic value of NLR within the same population.

2.3. Patient Selection and Inclusion/Exclusion Criteria

The study included patients aged 18 years and older diagnosed with Stage II-IVA esophageal cancer who were selected for Neoadjuvant CRT was administered to radiotherapy fields determined according to the primary tumor location of the patients. The median radiotherapy dose was recorded as 50.4 Gy (range: 41.4-54 Gy). The vast majority of patients received a chemotherapy regimen comprising 5 cycles of a carboplatin and paclitaxel combination. Between the 4th and 6th weeks following the completion of nCRT, clinical treatment response was evaluated using a combination of radiological, metabolic, and endoscopic imaging modalities. Following re-staging, surgical and successfully completed nCRT following a multidisciplinary tumor board decision. Patients were enrolled in the study regardless of whether they underwent surgical resection following nCRT. The NLR, evaluated as the primary prognostic variable in the study, was calculated from the most recent complete blood count results obtained within one week prior to the initiation of nCRT. As part of the inclusion criteria, it was essential that patients had uninterrupted follow-up at our center and complete accessibility to laboratory data. Exclusion criteria were defined as patients receiving definitive or palliative-intent treatment, those who failed to complete nCRT, patients lost to regular follow-up, and individuals with unavailable NLR data. Furthermore, to avoid introducing bias on systemic inflammatory markers, patients presenting with signs of active infection at the time of blood sampling or those with a history of medication use that could alter blood count parameters (e.g., systemic steroids or immunosuppressants) were also excluded from the study. The implementation of these strict exclusion criteria was intended to improve the homogeneity of the analyzed cohort and enhance the internal validity of the study.

2.4. Treatment Protocol

resection was performed on 53 patients who met the operability criteria. For the remaining 19 patients, surgical intervention could not be pursued due to reasons such as medical inoperability or patient refusal.

2.5. Response Assessment and Follow-up

Although the patients in the study were initially scheduled for a protocol of nCRT followed by surgery, 19 patients did not undergo surgery post-CRT.

To ensure evaluation standardization and patient homogeneity within the dataset, the clinical and radiological assessment

results obtained during the 4th to 6th weeks following the completion of nCRT were used as the baseline for treatment response analyses for all patients. Rather than relying on strict standalone criteria (such as RECIST or PERCIST), response was evaluated using an integrated multimodal approach incorporating computed tomography, PET-CT, and/or endoscopy.

This comprehensive synthesis was chosen to account for the clinical and radiological challenges of distinguishing true residual viable tumor from post-chemoradiation inflammatory changes, edema, or fibrosis. Subsequent to this initial assessment, patients were regularly followed up every 3 months post-treatment using appropriate imaging studies. The follow-up duration encompasses the period from the completion of treatment to the last assessment or death. Overall survival (OS) and progression-free survival (PFS) times were recorded for prognostic evaluation.

2.6. Statistical Analysis

Analyses were performed using R software (version 4.4.2). Normality was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests, supported by Q-Q plots and histograms.

Continuous variables were expressed as median (minimum-maximum) or mean ± standard deviation (SD), while categorical variables were presented as frequencies (%).

The Mann-Whitney U test was applied for independent continuous variables, and Pearson's Chi-square or Fisher's exact tests were utilized for categorical comparisons. The optimal NLR cut-off value was determined using maximally selected rank statistics (the "maxstat" package).

The Kaplan-Meier method and log-rank tests were used to compare survival outcomes.

Variables with a p value <0.20 in the univariate Cox regression analysis were entered into the multivariate Cox regression model, provided that the model assumptions were satisfied.

Model fit was assessed using the partial likelihood ratio test and the Akaike Information Criterion (AIC). Statistical significance was set at $p < 0.05$.

2.7. Ethical Considerations

This retrospective study was approved by the Başakşehir Çam ve Sakura City Hospital Ethics Committee (Approval No: [2024-214], Date: [17.09.2024]). Due to the retrospective design of the study, the requirement for written informed consent was waived by the ethics committee.

3. RESULTS

A total of 72 patients with esophageal cancer who received nCRT were included in the study. The baseline clinical and demographic characteristics of the patients are summarized in *Table 1*.

The median age was 60 years, and 35% of the patients (n=25) were aged 65 years or older. Most patients were female (67%), and 37 (51%) had at least one comorbidity. Thirty patients (42%) were ever smokers. The vast majority of the patients (84.7%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Histopathologically, squamous cell carcinoma was the predominant subtype, observed in 61 patients (85%), while adenocarcinoma was detected in 11 patients (15%).

Advanced T-stage disease (T3–T4) was present in 58 patients (81%), while lymph node involvement (N1–N3) was observed in 56 patients (78%). Regarding laboratory findings, the median white blood cell count was $7.67\times10^3/mm^3$ (3.55–13.12), the median neutrophil count was $4.55\times10^3/mm^3$ (2.37–10.54), and the

median lymphocyte count was $1.90\times10^3/mm^3$ (0.41–4.99). The median neutrophil-to-lymphocyte ratio (NLR) was 2.40 (0.81–8.12).

Upon evaluation of the treatment response following nCRT, complete or partial response (CR+PR) was observed in 62 patients (86%), whereas stable or progressive disease (SD+PD) was noted in 10 patients (14%). During the follow-up period, disease recurrence occurred in 24 patients (33%), and a total of 28 patients (39%) died.

A composite endpoint comprising recurrence or mortality was observed in 37 patients (51%). The median follow-up time for the entire cohort was 21 months (range: 1–49 months). At the time of analysis, the median overall survival (OS) was not reached, whereas the median progression-free survival (PFS) was 15 months(range: 1–49 months).

Table. Characteristics of Patients

Characteristics N = 72	Median/number (%)
Age, years	60 (20-93)
Gender	
Female	48 (67)
Male	24 (33)
Comorbidity	37 (51)
Ever Smoked	30 (42)
ECOG <2	61 (85)
Histological type	
Adenocarcinoma	11 (15)
SCC	61 (85)
Tumor location	
Thoracic	29 (40)
Distal	22 (31)
GEJ	8 (11)
Multiple areas	13 (18)
T stage	
T2	14 (19)
T3/4	58 (81)
N stage	
N0	16 (22)
N1-3	56 (78)
WBC, $10^3/mm^3$	7.67 (3.55-13.12)
Neutrophil, $10^3/mm^3$	4.55 (2.37-10.54)
Lymphocyte, $10^3/mm^3$	1.90 (0.41-4.99)
NLR	2.40 (0.81-8.12)
Radiotherapy dose, Gy	50.4 (41.4-54.0)
nCRT response	
CR+PR	62 (86)
SD+PD	10 (14)
Recurrence	24 (33)
Mortality	28 (39)
Recurrence/Mortality	37 (51)
Overall survival time, month	-
Progression free survival time, month	15 (1-49)

Data are presented as number (percentage) for categorical variables and as median (minimum-maximum) for continuous variables.

Based on maximally selected log-rank statistics, the optimal NLR cut-off value was determined as 2.4 for both OS and PFS *(Figure 1).*

Using this cutoff value, patients were stratified into two groups:

38 patients (53%) with an NLR ≤2.4 and 34 patients (47%) with an NLR >2.4.

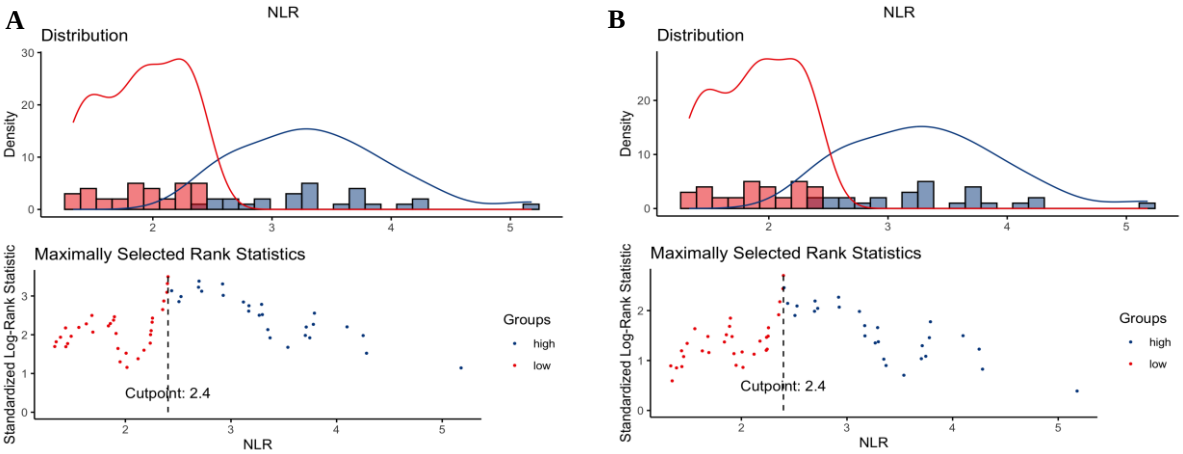

Figure1. Optimal NLR cut-off values determined using maximally selected rank statistics for (A) overall survival and (B) progression-free survival. The optimal cut-off point of NLR is 2.4.

Among the evaluated clinico pathological characteristics, only sex was significantly associated with NLR (p=0.019), with male patients exhibiting a higher rate of elevated NLR (>2.4) compared to females (67% vs. 33%). No significant associations were found between NLR and other clinico pathological parameters, including age, comorbidities, ECOG performance status, histological type, T stage, N stage, radiotherapy (RT) dose, and response to nCRT (Table 2).

According to Kaplan-Meier analysis, subgroup evaluation based on the optimal NLR cutoff showed significantly different survival outcomes. Patients in the high-risk group (NLR > 2.4) experienced significantly worse progression-free survival compared to those in the low-risk group (NLR ≤ 2.4) (p=0.013). Similarly, overall survival was significantly inferior in patients with an NLR > 2.4 compared to those with an NLR ≤ 2.4 (p<0.001) (Figure 2).

Table 1. Association of Pretreatment NLR with Patient and Treatment Characteristics

	NLR		
Characteristics	**≤2.4** N = 38	**>2.4** N = 34	**p-value**
Age			0.277[2]
<65	27 (57)	20 (43)	
≥65	11 (44)	14 (56)	
Sex			**0.019**[2]
Female	30 (63)	18 (38)	

Characteristics	NLR		
	≤2.4 N = 38	**>2.4** N = 34	**p-value**
Male	8 (33)	16 (67)	
Comorbidity			0.487[2]
Absent	17 (49)	18 (51)	
Present	21 (57)	16 (43)	
Smoking			0.690[2]
Ever smoked	15 (50)	15 (50)	
Never smoked	23 (55)	19 (45)	
Histological type			0.898[2]
Adenocarcinoma	6 (55)	5 (45)	
SCC	32 (52)	29 (48)	
Tumor location			0.644[3]
Thoracic	18 (62)	11 (38)	
Distal	10 (45)	12 (55)	
GEJ	4 (50)	4 (50)	
Multiple areas	6 (46)	7 (54)	
T stage			0.407[2]
T2	6 (43)	8 (57)	
T3/4	32 (55)	26 (45)	
N stage			0.752[2]
N0	9 (56)	7 (44)	
N1-3	29 (52)	27 (48)	
Radiotherapy dose, Gy	50.4 (45.0-50.4)	50.4 (50.0-50.4)	0.853[4]
nCRT response			>0.999[3]
CR+PR	33 (53)	29 (47)	
SD+PD	5 (50)	5 (50)	

Data are presented as number(percentage) for categorical variables and as median (minimum-maximum) for continuous variables.

2Pearson's Chi-squared test, 3Fisher's exact test, 4Mann-Whitney U test

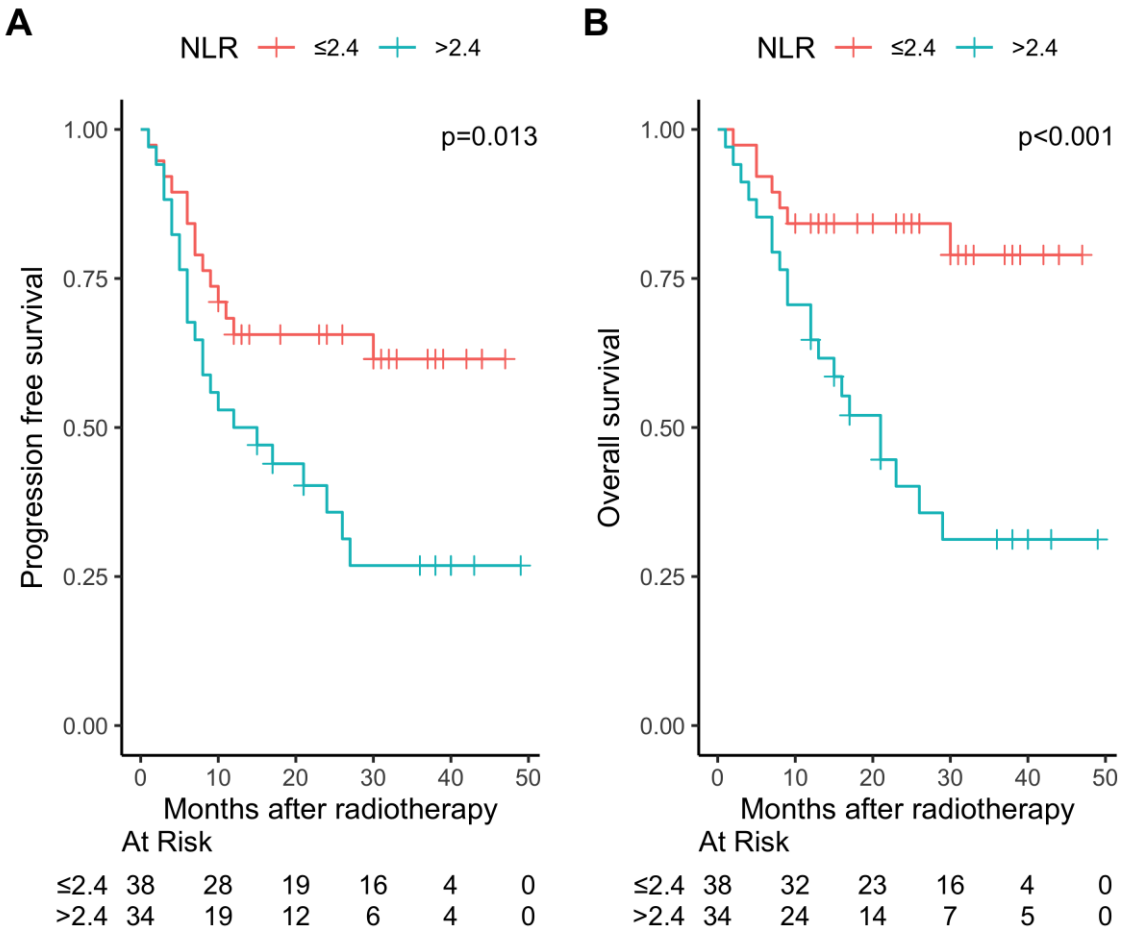

Figure 2. Association of Baseline NLR (≤2.4 vs >2.4) with Progression Free Survival (A) and Overall Survival (B)

In the univariate Cox regression analysis, smoking history (HR=2.14, 95% CI: 1.11–4.11, p=0.023), NLR >2.4 (HR=2.28, 95% CI: 1.17–4.44, p=0.016), and poor treatment response (SD+PD vs. CR+PR) (HR=3.01, 95% CI: 1.36–6.65, p=0.006) were significantly associated with worse progression-free survival. In the multivariate analysis, smoking history (HR=2.07, 95% CI: 1.05–4.11, p=0.036), NLR >2.4 (HR=2.18, 95% CI: 1.09–4.37, p=0.028), multi-segment tumor involvement (HR=4.01, 95% CI: 1.08–14.9, p=0.038), and poor response to nCRT (HR=3.20, 95% CI: 1.42–7.24, p=0.005) remained independent prognostic factors for progression-free survival (Table 3).

Table 2. Univariate and Multivariate Analysis of Factors Associated with Progression Free Survival

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65	1.19 (0.61-2.31)	0.610		
Male sex	1.47 (0.76-2.83)	0.253		
Comorbidity	1.50 (0.78-2.90)	0.226		

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Ever Smoked	2.14 (1.11-4.11)	**0.023**	2.07 (1.05-4.11)	**0.036**
Histological type-SCC	1.08 (0.45-2.60)	0.859		
Tumor location				
GEJ	—		—	
Thoracic	1.03 (0.28-3.75)	0.964	1.53 (0.41-5.76)	0.526
Distal	2.06 (0.59-7.19)	0.257	2.56 (0.71-9.22)	0.149
Multiple areas	3.59 (0.98-13.2)	0.054	4.01 (1.08-14.9)	**0.038**
Stage T3/4	0.96 (0.42-2.19)	0.927		
Lymph node involvement	1.30 (0.57-2.95)	0.538		
WBC	1.03 (0.90-1.18)	0.676		
Neutrophils	1.08 (0.91-1.28)	0.375		
Lymphocytes	0.88 (0.62-1.25)	0.481		
NLR >2.4	2.28 (1.17-4.44)	**0.016**	2.18 (1.09-4.37)	**0.028**
Radiotherapy dose, Gy	0.95 (0.86-1.06)	0.385		
nCRT response				
CR+PR	—		—	
SD+PD	3.01 (1.36-6.65)	**0.006**	3.20 (1.42-7.24)	**0.005**

HR = Hazard ratio, CI = Confidence interval,
GEJ=Gastroesophageal junction, nCRT = Neoadjuvant chemoradiotherapy,
CR = Complete response, PR = Partial response, SD = Stable disease,
PD = Progressive disease

In terms of overall survival, univariate analysis revealed that an NLR >2.4 was significantly associated with worse overall survival (HR=4.18, 95% CI: 1.77–9.87, p=0.001) (Table 4). Subsequent multivariate analysis confirmed that an NLR >2.4 was an independent factor adversely affecting overall survival (HR=2.23, 95% CI: 1.11–4.49, p=0.024). Furthermore, a poor treatment response (SD+PD vs. CR+PR) was identified as an independent variable significantly reducing overall survival (HR=3.34, 95% CI: 1.38–8.09, p=0.008).

Table 3. Univariate and Multivariate Analysis of Factors Associated with Overall Survival

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65	1.62 (0.77-3.41)	0.202		
Male sex	1.44 (0.68-3.05)	0.340		
Comorbidity	1.88 (0.87-4.08)	0.110	1.76 (0.85-3.65)	0.128
Ever smoked	1.58 (0.74-3.36)	0.236		
Histological type-SCC	0.96 (0.36-2.52)	0.927		
Tumor location				

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
GEJ	—		—	
Thoracic	1.39 (0.30-6.46)	0.673	0.93 (0.25-3.51)	0.919
Distal	1.90 (0.41-8.83)	0.411	1.61 (0.45-5.83)	0.465
Multiple areas	3.56 (0.75-16.9)	0.111	3.36 (0.92-12.3)	0.067
Stage T3/4	0.78 (0.32-1.92)	0.588		
Lymph node involvement	1.07 (0.43-2.64)	0.884		
WBC	1.02 (0.87-1.19)	0.832		
Neutrophil	1.13 (0.93-1.37)	0.214		
Lymphocyte	0.66 (0.42-1.04)	0.073		
NLR >2.4	4.18 (1.77-9.87)	**0.001**	2.23 (1.11-4.49)	**0.024**
Radiotherapy dose, Gy	0.96 (0.85-1.09)	0.559		
nCRT response				
CR+PR	—		—	
SD+PD	2.12 (0.79-5.66)	0.135	3.34 (1.38-8.09)	**0.008**

HR = Hazard ratio, CI = Confidence interval, GEJ=Gastroesophageal junction, nCRT = Neoadjuvant chemoradiotherapy, CR = Complete response, PR = Partial response, SD = Stable disease,
PD = Progressive disease

4. DISCUSSION

This study presents a retrospective analysis evaluating the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in patients with esophageal cancer who received nCRT.

Our findings demonstrate that an NLR cutoff value of >2.4, which exhibited a strong adverse impact on overall survival (OS) in univariate analysis (HR=4.18), remained associated as an independent prognostic factor for both OS (HR=2.23, 95% CI: 1.11–4.49, p=0.024) and PFS (HR=2.18, 95% CI: 1.09–4.37, p=0.028) in the multivariate analysis. These findings are consistent with the proposed role of systemic inflammation in cancer progression and suggest that pretreatment NLR may serve as a potential prognostic biomarker in patients with esophageal cancer receiving nCRT. However, the interpretation of our OS findings must be contextualized within the current follow-up period. Given the relatively short median follow-up time of 21 months, the median OS for the entire cohort was not reached, indicating that our OS data are still relatively immature. While the early and statistically significant divergence in the survival curves strongly suggests the adverse prognostic impact of an elevated NLR, these OS results require longer-term follow-up to fully establish their definitive clinical effect.

In the literature, the prognostic value of the NLR as a marker in solid tumors is increasingly acknowledged. A comprehensive systematic review and meta-analysis have revealed that the NLR is associated with poor survival across various solid tumors, and this relationship has been confirmed in a broad patient population, including esophageal cancer (14).

Similarly, the impact of systemic inflammation on cancer development and metastasis has been discussed in detail, with evidence indicating that inflammation enhances DNA damage and promotes angiogenesis (8). Our findings are consistent with these proposed biological mechanisms in patients receiving nCRT. Specifically, the observed association between an NLR >2.4 and poorer survival outcomes in our cohort is consistent with this biological rationale. A large-scale review encompassing over 60 studies and more than 37,000 patients emphasized that the NLR carries a consistent prognostic value, particularly in advanced-stage and treated cancer patients (12). This independent association with survival has also been robustly documented across various other distinct cohorts (14). Nevertheless, there are studies in the literature that have reported no association between the NLR and survival (15).

In our study, the optimal NLR cutoff value was determined to be 2.4, which falls within the range of cutoff values reported in previous studies. A meta-analysis on esophageal cancer reported that NLR cutoff values vary across studies (generally in the 2.0–5.0 range) and that this heterogeneity may stem from differences in treatment protocols and patient populations (19). The relatively homogeneous use of nCRT in our cohort may have contributed to the identification of this cutoff value, as baseline inflammatory status may interact with treatment response to chemoradiotherapy.

Existing literature, including earlier reports (20-22) and a recent comprehensive meta-analysis (23), predominantly suggests a strong association between elevated pre-treatment NLR and both a lower likelihood of achieving a pathological response and poorer survival in esophageal cancer patients undergoing neoadjuvant therapy. In contrast to these established findings, the pre-treatment NLR cut-off did not reach statistical significance in predicting objective response rates within our relatively small cohort ($p > 0.999$). However, the absence of a correlation with treatment response highlights another aspect of our findings: the prognostic impact of NLR on overall survival operates independently of the tumor's immediate response to nCRT. This suggests that pre-treatment NLR reflects broader systemic host-tumor immunodynamics that dictate long-term outcomes, irrespective of localized treatment efficacy.

Our multivariate survival analysis supports this independence. While the validation of treatment response as a strong prognostic factor for both PFS and OS was an expected finding consistent with our previous work (18).

We observed that an NLR >2.4 retained its independent prognostic value even when treatment response and smoking history were simultaneously included in the multivariate model. This indicates that NLR can provide prognostic information alongside standard clinical parameters.

This observation is also consistent with the prognostic heterogeneity recognized in the current 8th edition TNM staging system, where patients within the same stage may experience different survival outcomes. Our findings further support the potential value of incorporating additional prognostic biomarkers alongside conventional staging systems (7).

Despite the broad association suggested by pooled data, literature specific to esophageal cancer contains notable inconsistencies regarding the prognostic value of the NLR. While its prognostic role is well established in several other gastrointestinal malignancies (16,24–27).

The prognostic significance of NLR in esophageal cancer remains less consistent. Although most studies have reported an adverse prognostic impact of elevated NLR, negative findings have also been described, particularly in operable cohorts (15,19). These contradictions largely stem from differences in patient selection, treatment regimens, and NLR cutoff values across studies. Restricting our cohort to patients treated exclusively with nCRT may have reduced treatment-related heterogeneity, thereby allowing a more homogeneous evaluation of the prognostic value of pretreatment NLR.

However, the retrospective nature, limited sample size (n=72), and relatively short follow-up time of our study restrict the generalizability of our results. While the identification of the same optimal cutoff value (2.4) for both OS and PFS suggests internal consistency in our analysis, the fact that this threshold was internally derived using maximally selected log-rank statistics is a methodological limitation. As this approach may yield statistically overly optimistic (overfitting) results in small samples, the obtained cutoff value of 2.4 requires external validation in larger, independent cohorts for clinical practice. Furthermore, contrary to the well-known male predominance in the literature, the high proportion of female patients (67%) in our cohort is related to the specific patient referral profile and regional demographic characteristics of our center. Nevertheless, although the data were obtained from a single center, the relatively homogeneous treatment approach across the study population may have improved the internal validity of our analyses.

5. CONCLUSION

In this single-center retrospective cohort, higher pretreatment NLR was associated with poorer OS and PFS after adjustment for selected clinical variables. Because the cutoff was derived and evaluated in the same small cohort, and because treatment pathways included both surgery and non-surgical management, the findings should be considered exploratory. External validation using NLR as a continuous variable and adequately powered prospective cohorts is required before clinical implementation.

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