Original Article

Predicting prognosis of locally advanced esophageal squamous cell carcinoma through early changes in neutrophil-to-lymphocyte ratio following neoadjuvant immunochemotherapy

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Background: The effectiveness of neoadjuvant immunochemotherapy (NAIC) in locally advanced esophageal squamous cell carcinoma (ESCC) remains unclear. This study aims to validate the relation between early alterations in neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes among individuals diagnosed with locally advanced ESCC undergoing NAIC.

Methods: We retrospectively enrolled a cohort of ESCC patients who underwent NAIC at least 1 cycle between May 2020 and October 2021 at Guangdong Provincial People's Hospital. Blood tests were conducted both at the baseline and following the initial treatment cycle. We examined the correlation between NLR-Δ [(cycle 1 NLR – baseline NLR)/baseline NLR × 100%] and overall survival (OS) in ESCC patients.

Results: Ninety-eight patients were enrolled in this study, with a median patient age of 62 years [interquartile range (IQR), 56.0–67.0 years]. The median baseline NLR was 2.63 (1.09–9.23). A total of 39 mortality events were observed after a median follow-up of 37.55 months. Thirty-three patients (33.67%) had NLR-Δ ≤–35%, while 65 patients (66.33%) had NLR-Δ >–35%, patients with NLR-Δ ≤–35% (N=33) exhibited significantly worse OS compared to patients with NLR-Δ >–35% (N=65) (median OS: 28.330 months *vs.* unreached, P=0.044). The independent prognostic factors for OS in this cohort of patients diagnosed with ESCC were NLR-Δ and the receipt of surgical treatment.

Conclusions: Patients with a decrease in NLR value of more than 35% after the first cycle of immunochemotherapy may be associated with a worse clinical outcome in ESCC. NLR-Δ shows potential as an early-detection biomarker for NAIC-treated ESCC.

Keywords: Esophageal squamous cell carcinoma (ESCC); immunochemotherapy; neutrophil-to-lymphocyte ratio (NLR); predictive biomarker

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Introduction

The advent of immune checkpoint inhibitors (ICIs) has brought about a revolutionary shift in the treatment paradigm for advanced esophageal squamous cell carcinoma (ESCC) (1-4). However, responses to neoadjuvant immunochemotherapy (NAIC) vary, and dismal prognosis remains a major clinical challenge for non-responders. There is a critical need for easily accessible, low-cost, and relatively non-invasive biomarkers with high predictive capability to assist physicians in identifying which kind of locally advanced ESCC patients may benefit from NAIC.

Multiple studies have consistently shown a strong association between tumor-related inflammatory responses and the initiation, progression, and metastasis of malignancies (5,6). The inflammatory microenvironment within a developing tumor encompasses diverse leukocyte populations, which secrete cytokines and cytotoxic agents. Circulating inflammatory cells also discharge factors that facilitate tumor proliferation, angiogenesis, and invasion (7).

Several inflammation-associated hematological parameters, including the absolute eosinophil count (AEC) (8), absolute lymphocyte count (ALC) (9), and derived neutrophil-to-lymphocyte ratio (dNLR) (10) have been elaborated as effective markers for predicting immunotherapy efficacy in patient prognosis with solid cancer. These studies focused on the relationship between baseline values of peripheral blood inflammatory cells and clinical outcomes, however, recently there has been an increasing number of studies focused their sights on trajectory changes. Guven *et al.* report that changes in blood-based biomarkers, specifically the neutrophil-to-lymphocyte ratio (NLR), function as a prognostic indicator in patients undergoing treatment with ICIs. Elevated NLR and a rise in NLR by 10% or more during the fourth week of treatment were linked to a decline in overall survival (OS) (11). Chen *et al.* demonstrated that dynamic changes of NLR were strongly associated with treatment outcomes and prognosis in patients with non-small cell lung cancer undergoing immunotherapy (12).

Based on these findings, we proposed that dynamic changes of blood count trajectories can reflect the alterations in microenvironment during the ICI treatment. In this study, we aimed to examine the association of early NLR changes and the clinical outcomes of ESCC patients treated with NAIC. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1115/rc).

Highlight box

Key findings

- Patients with a decrease in neutrophil-to-lymphocyte ratio (NLR) value of more than 35% after the first cycle of immunochemotherapy may be associated with a poorer clinical outcome in esophageal squamous cell carcinoma (ESCC).

What is known and what is new?

- Several baseline inflammation-associated hematological parameters, including the absolute eosinophil count, absolute lymphocyte count, and NLR have been elaborated as effective markers for predicting immunotherapy efficacy in patient prognosis with solid cancer.
- While peripheral blood inflammatory markers assessed at baseline can predict the efficacy of immunotherapy, dynamic monitoring of these markers provides a more accurate reflection of immune system change and better predicts the outcomes of immune-related treatments.

What is the implication, and what should change now?

- NLR-Δ shows potential as an early-detection biomarker for neoadjuvant immunochemotherapy-treated ESCC.

Methods

Patients and study design

The present study received approval from the ethics committee at Guangdong Provincial People's Hospital [No. GDREC2020195H(R1)]. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Before engagement, all participating patients appropriately provided explicit and informed consent.

In this observational study, we retrospectively enrolled patients with ESCC and received NAIC between May 2020 and October 2021 at the Department of Thoracic Surgery, Guangdong Provincial People's Hospital. Eligible patients were pathologically confirmed ESCC before treatment and have radiologically estimated resectable or had the potential for resection (cT3–4aN0–3M0). Patients were treatment-naive, without significant organ dysfunction. Patients with a history of cervical esophageal cancer, multiple primary esophageal cancers, or other malignant tumors or had previous anti-tumor treatment were excluded from this study (*Figure 1*). Clinical characteristics, such as gender, age at the start of treatment, type of pathology, stage of the disease, smoking and alcohol history, family cancer history, number of comorbidity, tumor location, and treatment regimen, were extracted from electronic medical records.

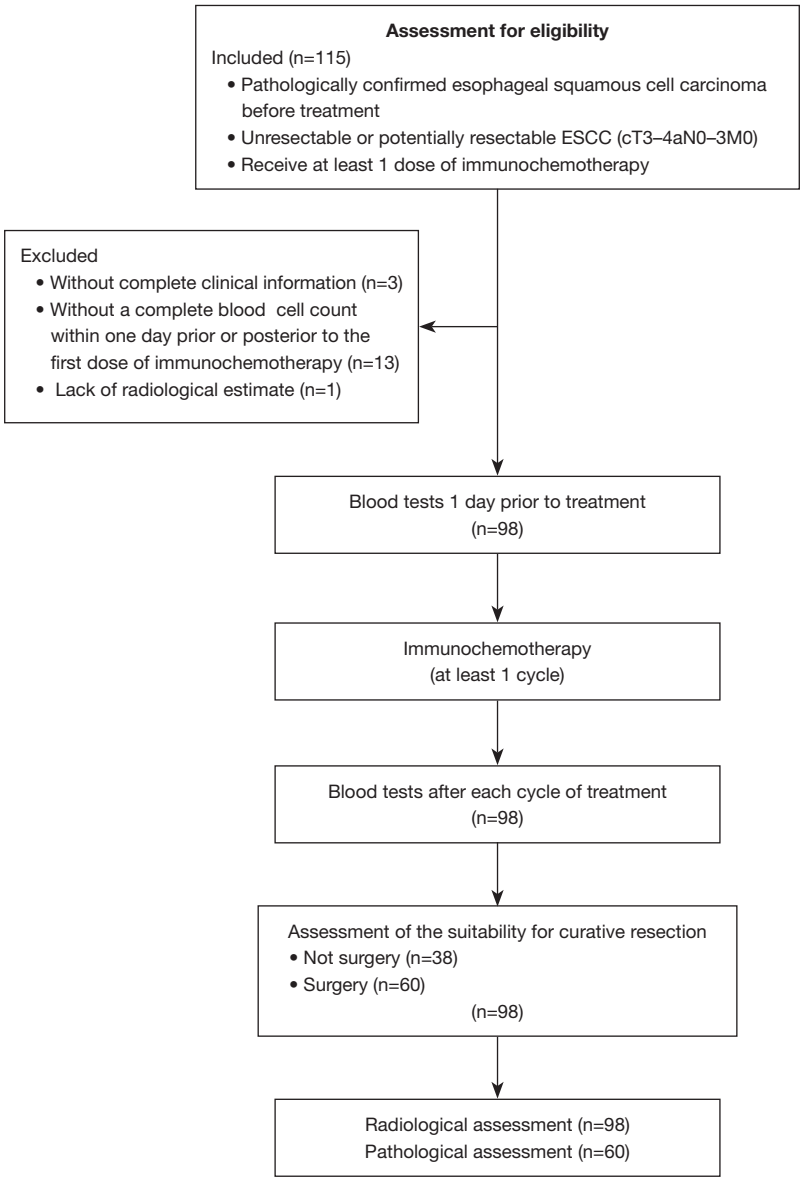

Figure 1 Flowchart of the study design. Blood tests for the eligible patients were performed at baseline (within 1 day prior to the first cycle) and after each treatment cycle. Assessment for curative resection suitability occurred following at least one cycle of NAIC, followed by imaging and pathological evaluations at the treatment's conclusion. ESCC, esophageal squamous cell carcinoma; NAIC, neoadjuvant immunochemotherapy.

Treatment regimen

All patients received at least one cycle of NAIC (the treatment regimen in this study consisted of administering programmed cell death 1 (PD-1) inhibitors and chemotherapy agents intravenously every 3 weeks. The PD-1 inhibitors included tislelizumab (200 mg), pembrolizumab (200 mg), camrelizumab (200 mg), sintilimab (200 mg), and nivolumab (240 mg). The chemotherapy regimen was based on platinum compounds combined with either docetaxel or taxane-based agents, with doses adjusted according to the patient's body surface area and liver and renal function), and underwent disease evaluation with contrast-enhanced chest and abdominal computed tomography (CT) or positron emission

tomography (PET)/CT after three or four weeks. Patients who met the surgical criteria and were willing to undergo surgery received either a McKeown esophagectomy or an Ivor Lewis esophagectomy, involving appropriate lymphadenectomy procedures.

Blood tests were conducted within 1 day before the first treatment (baseline-NLR), and 1 day before the second treatment (for patients receiving only one cycle, the blood draw was conducted 20 days after the first treatment) (C1NLR).

Data assessment

NLR value was defined as the absolute count of neutrophils divided by the absolute count of lymphocyte, bNLR was defined as the baseline NLR, NLR-Δ was defined as the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value. Optimal cutoff values for NLR-Δ were selected to maximize differences of OS based on the Kaplan-Meier curve and log-rank test (13). In studies of similar nature, no specific cut-off value was identified, we selected −35% as the cut-off value and categorize the enrolled patients into two groups by −35%. NLR-Δ ≤−35% represents a decrease in NLR of greater than or equal to 35%, whereas NLR-Δ >−35% represents a decrease in NLR of less than 35%.

$$NLR\text{-}\Delta = \frac{C1NLR - bNLR}{bNLR} \times 100\% \quad [1]$$

Radiological response was assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (14). The objective response rate (ORR) was determined as the combined proportion of complete response (CR) and partial response (PR). The disease control rate (DCR) was defined as the combined proportion of CR, PR, and stable disease (SD). Pathological complete response (pCR) was described as the absence of viable tumors in both the primary tumor and resected lymph nodes, while major pathological response (mPR) was defined as less than or equal to 10% residual viable tumor within the primary tumor bed. OS was calculated from the initiation of NAIC to the date of patient death or the conclusion of follow-up.

Statistical analysis

Mann-Whitney test and Pearson's Chi-squared test were applied to perform intergroup comparisons. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of OS. Variables were only included in multivariable Cox regression if survival effects were significant in univariate analysis (P<0.10). Kaplan-Meier plots and log-rank tests were used to compare survival. A significance level of P<0.05 was employed for statistical analysis. Statistical analyses were conducted employing the IMB SPSS version 26 and R version 4.0.0 (R Core Team 2020).

Results

Clinicopathological characteristics

Ninety-eight patients were enrolled in the study. Detailed baseline clinical characteristics are presented in *Table 1*. The median age of the patients was 62 years [interquartile range (IQR), 56.0–67.0 years], 67 patients (68.37%) aged over 65 years, and 79 (80.6%) were male. Among the patients, 31 had comorbidities, with 25 patients having only one comorbidity, 5 patients having two comorbidities, and 1 patient having three comorbidities. Sixty patients (61.22%) underwent esophagectomy. No significant differences were observed in terms of age, gender, family history of ESCC, number of comorbidity, clinical staging, and treatment regimen between NLR-Δ ≤−35% group and NLR-Δ >−35% group. The distinct variations in NLR throughout the treatment courses are visually depicted in *Figure 2*, which provides a comprehensive overview of how NLR evolves in response to the treatment regimen over time. The red line represents individuals with NLR-Δ ≤−35%, while the grey line represents individuals with NLR-Δ >−35%.

Overall treatment response

Among the included ESCC patients, 5 patients (5.1%) achieved CR, and 65 patients (66.33%) achieved PR. The ORR and DCR were 71.43% and 87.76% respectively. Moreover, among the 60 patients who underwent esophagectomy, the median interval from the final NAIC to surgery was 38 days, for patients in the NLR-Δ ≤−35% group, the median interval was 37 days, while for those in the NLR-Δ >−35% group, it was 39 days. A total of 12 patients (20%) achieved pCR status, and 24 patients (24.5%) achieved mPR status.

Treatment response by NLR-Δ

The optimal cutoff value for NLR-Δ was −35%. In this study, 33 patients (33.67%) had NLR-Δ ≤−35%, and

Table 1 Baseline characteristics of patients with locally advanced esophageal squamous cell carcinoma in the study

Characteristics	NLR-Δ ≤−35% (N=33)	NLR-Δ >−35% (N=65)	Overall (N=98)	P value
Sex				0.30
Female	4 (12.1)	15 (23.1)	19 (19.4)	
Male	29 (87.9)	50 (76.9)	79 (80.6)	
Age, years				
Median (IQR)	60.0 (56.0–64.0)	62.0 (56.0–68.0)	62.0 (56.0–67.0)	0.41
>65	25 (75.8)	41 (63.1)	67 (68.37)	0.30
Smoking history				0.88
Never smoker	18 (54.5)	33 (50.8)	51 (52.0)	
Previous smoker	15 (45.5)	32 (49.2)	47 (48.0)	
Drinking history				0.89
Never drinker	20 (60.6)	37 (56.9)	57 (58.2)	
Previous drinker	13 (39.4)	28 (43.1)	41 (41.8)	
Family history				0.62
Family history	5 (15.2)	14 (21.5)	19 (19.4)	
No family history	28 (84.8)	51 (78.5)	79 (80.6)	
Number of comorbidity				0.29
0	19 (57.6)	48 (73.8)	67 (68.37)	
1	12 (36.4)	13 (20.0)	25 (25.51)	
2	2 (6.1)	3 (4.6)	5 (5.10)	
3	0	1 (1.5)	1 (1.02)	
Tumorlocation				0.03
Upper portion	6 (18.2)	8 (12.3)	14 (14.3)	
Middle portion	20 (60.6)	25 (38.5)	45 (45.9)	
Lower portion	7 (21.2)	32 (49.2)	39 (39.8)	
cT				0.44
3	26 (78.8)	45 (69.2)	71 (72.4)	
4a	7 (21.2)	20 (30.8)	27 (27.6)	
cN				0.75
0	8 (24.2)	21 (32.3)	29 (29.6)	
1	20 (60.6)	38 (58.5)	58 (59.2)	
2	4 (12.1)	5 (7.7)	9 (9.2)	
3	1 (3.0)	1 (1.5)	2 (2.0)	
cTNM				0.55
II	6 (18.2)	14 (21.5)	20 (20.4)	
III	19 (57.6)	30 (46.2)	49 (50.0)	
IVA	8 (24.2)	21 (32.3)	29 (29.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	NLR-Δ ≤–35% (N=33)	NLR-Δ >–35% (N=65)	Overall (N=98)	P value
Treatment regimen				0.88
Chemo + camrelizumab	7 (21.2)	19 (29.2)	26 (26.5)	
Chemo + nivolumab	2 (6.1)	3 (4.6)	5 (5.1)	
Chemo + pembrolizumab	13 (39.4)	22 (33.8)	35 (35.7)	
Chemo + sintilimab	7 (21.2)	11 (16.9)	18 (18.4)	
Chemo + tislelizumab	4 (12.1)	10 (15.4)	14 (14.3)	

Data are presented as n (%) unless otherwise specified. NLR, neutrophil-to-lymphocyte ratio; NLR-Δ, the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value; IQR, interquartile range; TNM, tumor-node-metastasis; Chemo, chemotherapy regimen, which was based on platinum compounds combined with either docetaxel or taxane-based agents.

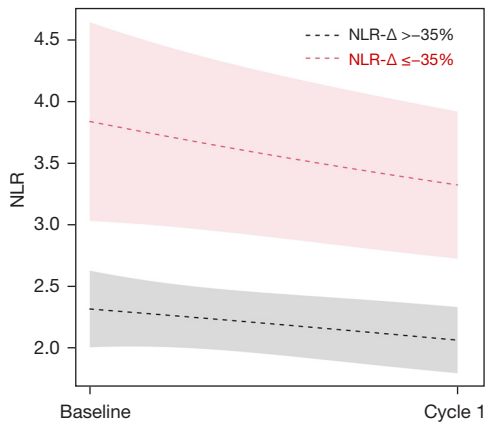

Figure 2 Longitudinal trend of NLR during NAIC treatment. Patients with NLR-Δ ≤-35% are represented by the red line while patients with NLR-Δ >–35% are represented by the grey line. NLR, neutrophil-to-lymphocyte ratio; NLR-Δ, the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value; NAIC, neoadjuvant immunochemotherapy.

65 patients (66.33%) had NLR-Δ >–35%. In the NLR-Δ ≤–35% group, 3 patients (9.09%) reached CR, and 22 patients (66.67%) achieved PR. The ORR was 75.76%, and the DCR was 90.91%. In the NLR-Δ >–35% group, 2 patients (3.08%) achieved CR, 43 patients (66.15%) reached PR. The ORR was 69.23%, and the DCR was 86.15%. There were no significant differences observed in terms of ORR or DCR between the two groups.

Survival outcomes

There were 39 deaths (40%) with a median follow-up time of 37.55 months, Through Cox regression analysis, we identified that NLR-Δ [≤–35% *vs.* >–35%, hazard ratio (HR) =1.942, 95% confidence interval (CI): 1.020–3.698] was an independent prognostic factor for OS (*Table 2*). Patients with NLR-Δ ≤–35% (NLR decrease of ≥35%) were associated with a worse OS than patients with NLR-Δ >–35% (NLR decrease of <35%) (median OS: 28.330 months *vs.* unreached, P=0.044) (*Figure 3*). In a univariate Cox regression subgroup analysis regarding whether patients with bNLR ≥2.63 and comorbidities have the same survival outcomes as those without comorbidities, it was found that there is no significant difference in survival outcomes between bNLR ≥2.63 patients with comorbidities and those without. Similarly, the results were consistent for patients with bNLR <2.63 (*Table 3*).

Discussion

Immunotherapy has transformed the therapeutic landscape for advanced esophageal cancer. yet the question of which patients stand to benefit the most remains. It has been reported that circulatory immune cell analysis could predict the effectiveness of tumor immunotherapy (8-12). However, the predictive role of early changes of NLR in locally advanced ESCC receiving NAIC remains unclear. This study employs a straightforward method capable of reflecting the trend in early changes of NLR to predict the treatment efficacy. In this study, we have preliminarily identified that NLR-Δ was an independent prognostic factor for OS. Notably, patients with an NLR-Δ of ≤–35% (NLR decrease of ≥35%) appeared to have poorer OS.

NLR, reflecting the combined levels of neutrophils and lymphocytes, serves as an indicator of the body's

Table 2 Univariable and multivariable Cox regression analysis for overall survival of patients with locally advanced esophageal squamous cell carcinoma

Variables	Univariable model			Multivariable model		
	HR	95% CI	P value	HR	95% CI	P value
Age (≥65 *vs.* <65 years)	1.395	0.68–2.865	0.36			
Sex	1.90	0.743–4.860	0.18			
Smoking history	1.291	0.685–2.433	0.42			
Drinking history	1.303	0.683–2.488	0.42			
Family history	2.487	0.882–7.007	0.08	1.923	0.626–5.907	0.25
Comorbidity	1.462	0.712–3.002	0.30			
Clinical TNM stage	1.033	0.664–1.605	0.88	0.703	0.191–2.585	0.59
Clinical T stage	1.041	0.517–2.093	0.91	2.365	0.392–14.267	0.34
Clinical N stage	1.015	0.647–1.592	0.94	0.669	0.295–1.521	0.33
Tumor location						
Upper portion	1					
Middle portion	0.448	0.191–1.050	0.06			
Lower portion	0.498	0.222–1.118	0.09			
bNLR (<2.63 *vs.* ≥2.63)	0.688	0.365–1.298	0.24			
NLR-Δ (≤–35% *vs.* >–35%)	1.892	1.006–3.557	0.048	1.942	1.020–3.698	0.043
Underwent surgery	0.183	0.094–0.360	<0.001	0.166	0.027–1.033	<0.001

HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; bNLR, baseline neutrophil-to-lymphocyte ratio; NLR-Δ, the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value; NLR, neutrophil-to-lymphocyte ratio.

inflammatory response. Recent studies suggest a close connection between tumor-associated inflammation, the tumor microenvironment, and cancer occurrence, development, and prognosis. Gungabeesoon *et al.* uncovered that the interferon gene signature in therapy-elicited neutrophils is essential for successful immunotherapy, the neutrophil response is contingent upon pivotal elements of anti-tumor immunity and manifests a correlation with the disease outcome in patients with lung cancer, researchers also assessed alterations in the NLR and the prognosis of patients with small cell lung cancer in clinical trials, both before and after chemotherapy, by monitoring NLR in peripheral blood. The findings indicated that patients with elevated baseline NLR (>2.5) at initial treatment had a poorer prognosis. However, those whose NLR increased (>10% increase versus baseline) after treatment experienced significantly longer progression-free survival (PFS) compared to those with decreased NLR (<10% increase versus baseline) levels (15), which is close to our result.

There are some studies with similar methodology, but with different results, Lalani *et al.* showed that the decreased NLR at the sixth week after treatment tended to have improved outcomes in metastatic renal cell carcinoma and advanced non-small cell lung cancer (16). Viñal *et al.* reported that PFS and OS were significantly extended in patients exhibiting an NLR trend <1 compared to those with an NLR trend ≥1 in advanced cancer patients receiving immunotherapy (17). Cassidy *et al.* calculated the NLR at baseline and at 3-week intervals in melanoma patients undergoing ipilimumab treatment, revealing an association between an NLR value of ≥5 at each timepoint and unfavorable outcomes (18). Dusselier *et al.* assessed the NLR changes between baseline and 4th nivolumab infusions and found that ΔNLR <1 prolonged OS (19). These studies tend to suggest that decreased NLR is associated with better clinical outcomes. However, the association between NLR and survival during immunotherapy is likely not characterized by a linear relationship but rather exhibits a

curvilinear or polynomial linear function (13), which is close to our result, we find that a rapid decrease of more than 35% in NLR after the first treatment cycle may suggest a poorer outcome, compared to previous similar studies, this study is more precise in predicting the range of NLR values. Moreover, we performed the first analysis of the change of NLR between baseline and the first cycle of NAIC in ESCC. The first-cycle NLR rate of change can identify whether patients with advanced esophageal cancer will benefit from NAIC at a much more early phase, compared to the NLR value change observed after two cycles or other timepoint (20-22). Moreover, NLR values are more readily available and relatively noninvasive compared to other proven biomarkers.

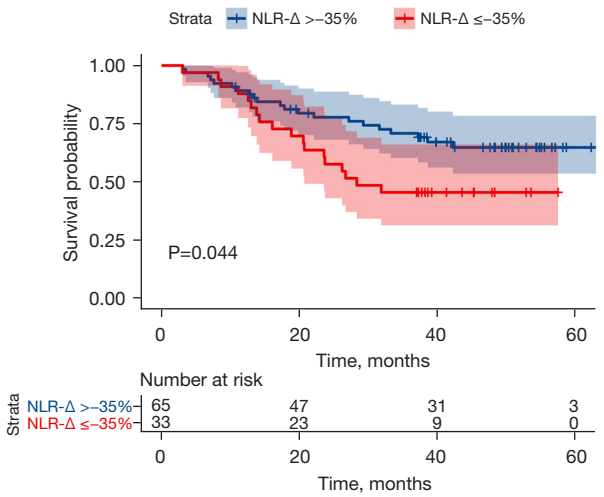

Figure 3 Kaplan-Meier plot for OS. NLR rate of change at the optimal cutoff value. Patients were stratified based on NLR-Δ with NLR-Δ ≤−35% represented by the red line and NLR-Δ >−35% represented by the blue line. A decrease in NLR exceeding 35% after the first cycle compared to baseline was associated with a poorer prognosis. NLR, neutrophil-to-lymphocyte ratio; NLR-Δ, the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value; OS, overall survival.

However, there are currently no trials specifically addressing interventions for patients with abnormal changes in NLR values during NAIC, who may have poorer prognoses. Based on the results of this study, NLR-Δ ≤−35% may result from either a decrease in neutrophil count or an increase in lymphocyte count. However, decreased neutrophil counts are more common. According to the NCCN guidelines (23), interventions for chemotherapy-induced neutropenia can be divided into prophylactic and therapeutic use of granulocyte colony-stimulating factor (G-CSF) and dose reduction of chemotherapeutic agents. Before the first treatment cycle, a risk assessment for febrile neutropenia [FN, an axillary temperature >38.5 ℃ for >1 hour with an absolute neutrophil count (ANC) <0.5×10^9/L] should be conducted, considering the chemotherapy regimen and patient risk factors. Prophylactic G-CSF should be considered for patients at intermediate or high risk. Before subsequent treatment cycles, FN risk should also be reassessed. For patients who have experienced FN or dose-limiting neutropenic events (which may affect chemotherapy dosing schedules) and previously used G-CSF, dose reduction or treatment regimen modification should be considered. Patients who have not previously used G-CSF can use it prophylactically. For patients who develop FN during treatment cycles, those receiving prophylactic filgrastim or tbo-filgrastim should continue G-CSF. Patients not on prophylactic G-CSF with risk factors for infection-

Table 3 Univariate Cox regression analysis of patient overall survival based on bNLR median value of 2.63 and comorbidity status

Variables	bNLR <2.63			bNLR ≥2.63		
	HR	95% CI	P value	HR	95% CI	P value
NLR-Δ ≤−35%						
With comorbidity	0.737	0.122–4.461	0.74	1.048	0.342–3.209	0.93
Without comorbidity	1			1		
NLR-Δ >−35%						
With comorbidity	0.644	0.141–2.942	0.57	0.194	0.024–1.558	0.123
Without comorbidity	1			1		

bNLR, baseline neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval; NLR-Δ, the rate of changes between the NLR value after the first treatment cycle relative to the baseline NLR value; NLR, neutrophil-to-lymphocyte ratio.

related complications should consider therapeutic use of marrow growth factors (MGFs). However, there is currently no definitive conclusion on the types, doses, and duration of G-CSF or MGFs use, and whether dose reduction of chemotherapeutic drugs during neutropenia affects the efficacy of NAIC in malignancies. Large-scale clinical trials are needed to address these issues in the future.

There are inevitably some limitations in this study, including its retrospective nature and the limited sample size, which to some extent constrain our analytical processes. Moreover, other indicators like C-reactive protein were not included in this study, which have proven its predictive value in tumor immunotherapy. Further research can explore the integration of serum indices with other established biomarkers and analyze their association with the prognosis of tumor immunotherapy. In the future, it is advisable to implement more frequent assessments per treatment cycle and employ trajectory plots to better forecast treatment efficacy.

Conclusions

This study preliminarily suggests that patients with patients with a decrease in NLR value of more than or equal to 35% after the first cycle of immunochemotherapy may be associated with a poorer clinical outcome in ESCC. However, these findings require further validation through large-scale prospective trials. Nonetheless, the application of NLR trend analysis may provide clinicians with a potential tool for predicting treatment outcomes for patients with locally advanced ESCC receiving NAIC. Furthermore, it presents a opportunity for targeted intervention following the initial treatment cycle for patients identified as having a potentially unfavorable prognosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1115/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1115/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1115/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Hslsinki (as revised in 2013). The study was approved by ethics committee at Guangdong Provincial People's Hospital [No. GDREC2020195H(R1)] and informed consent was taken from all the patients.

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