

Neutrophil-to-Lymphocyte Ratio After Definitive Concurrent Chemoradiotherapy Predicts Survival in Patients With Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim:* Lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio represent systemic immune-inflammatory responses. We evaluated the association between immune-inflammatory cell ratios and prognosis in esophageal squamous cell carcinoma (ESCC) patients who underwent definitive concurrent chemoradiotherapy (dCCRT). *Patients and Methods:* Medical records of 68 ESCC patients in three institutions who underwent dCCRT between 2006 and 2017 were reviewed. The immune-inflammatory cell ratios were calculated before and after dCCRT. *Results:* The median follow-up time was 11.4 months. The 3-year overall survival (OS) rate was 21.6%. Among the immune-inflammatory cell ratios, lower post-dCCRT neutrophil-to-lymphocyte ratio (NLR_{post}) was associated with better OS (median 15.2 vs. 9.7 months, $p=0.030$). Patients with lower NLR_{post} had more improved OS when adjuvant chemotherapy was administered following dCCRT (median 16.6 vs. 4.8 months,

$p<0.001$). *Conclusion:* NLR_{post} may be useful in predicting OS in ESCC patients after dCCRT. Furthermore, NLR_{post} might play a role in establishing adjuvant therapy plans following dCCRT.

Immune cells play important roles in the tumor microenvironment (TME). In the TME, tumor cells can have conflicting courses depending on the immune cells that interact with each other. Innate immune cells execute anti-tumor activity by initiating inflammation after sensing pathogen-associated or danger-associated molecular patterns. However, malignant cells are not eradicated in the TME under chronic inflammation (1). Chronic inflammation contributes to the proliferation and survival of malignant cells, angiogenesis, and metastasis (2). The inhibited anti-tumor immunity was caused by immunosuppressive cells, mitogenic growth factors, and cytokines, such as myeloid-derived suppressor cells, regulatory T cells, and transforming growth factor- β (3).

Evaluation of TME could be helpful for the assessment of prognosis in cancer patients. However, there would be difficulty in acquiring tissues from the tumor origin given the patient's convenience and anatomical risks. Lymphocytes, monocytes, neutrophils, and platelets are essential components of inflammation and immune responses, which can be tested easily and economically using peripheral blood. Lymphocyte-based indices, such as lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), are known to be surrogate markers of systemic immune-inflammatory responses. In many solid tumors, the prognostic value of LMR, NLR, and PLR has been reported (4-7).

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Table 1. Patient characteristics and univariate analysis.

Variables		N	(%)	Median OS (months)	p-Value
Age (year)	≤65	31	(45.6)	17.4	0.031
	>65	37	(54.4)	10.0	
Gender	Female	4	(5.9)	13.7	0.707
	Male	64	(94.1)	11.1	
Location	Lower	18	(26.5)	12.3	0.256
	Upper-middle	50	(73.5)	10.9	
T stage	T1-2	17	(25.0)	96.0	0.007
	T3-4	51	(75.0)	10.4	
N stage	N0-1	37	(54.4)	14.6	0.001
	N2-3	31	(45.6)	9.1	
Performance status	ECOG 0-1	54	(79.4)	11.4	0.710
	ECOG 2-3	14	(20.6)	12.7	
BED (cGy)	≤6372	32	(47.1)	11.1	0.357
	>6372	36	(52.9)	13.6	
Adjuvant chemotherapy	No	14	(20.6)	4.5	<0.001
	Yes	54	(79.4)	14.6	
LMRpre	≤5.75	60	(88.2)	10.7	0.020
	>5.75	8	(11.8)	Not reached*	
NLRpre	≤2.50	34	(50.0)	16.6	0.012
	>2.50	34	(50.0)	9.7	
PLRpre	≤83.1	8	(11.8)	6.7	0.067
	>83.1	60	(88.2)	13.4	
LMRpost	≤2.51	53	(77.9)	10.4	0.018
	>2.51	15	(22.1)	33.1	
NLRpost	≤5.44	42	(61.8)	15.2	0.030
	>5.44	26	(38.2)	9.7	
PLRpost	≤372.2	39	(57.4)	13.3	0.022
	>372.2	29	(42.6)	10.0	

*The 3-year overall survival rate is 56.2%. OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; BED: biologically effective dose; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Definitive concurrent chemoradiotherapy (dCCRT) is the mainstay treatment for esophageal squamous cell carcinoma (ESCC). Radiotherapy (RT) reduces peripheral blood cell counts, especially lymphocytes, which are more radio-sensitive than other leukocytes (8). Chemotherapy adversely affects the hematopoietic system, and neutropenia is one of the most serious hematologic toxicities of the treatment (9). With regards to the effect of RT and chemotherapy on immune-inflammatory responses, we aimed to compare the predictive value of LMR, NLR, and PLR measured before and after dCCRT in ESCC patients.

Patients and Methods

This study was performed by three institutions under the approval of the Institutional Review Board (IRB) of each participating hospital. Each IRB approved a waiver for informed consent. Details regarding data collection are described in a previous report (10). Information on 73 patients who underwent dCCRT for ESCC between 2006 and 2017 were reviewed. We collected lymphocyte, monocyte, neutrophil, and platelet counts within a week before the start and after the completion of RT. One patient with insufficient laboratory data was excluded. Given the potential effects of

chemotherapy on the blood cell count, four patients who received chemotherapy prior to the start of RT were excluded. Finally, 68 patients were included in the present study.

The data we collected for this study comprised patient and tumor characteristics, clinical information, treatment details, and the blood cell count. The locations of the primary tumors were categorized according to their distance from the upper incisors: upper thoracic (≤24 cm from the upper incisor), middle thoracic (≤32 cm from the upper incisor), and lower thoracic (>32 cm from the upper incisor). The leukocyte count was measured in cells per microliter (cells/μl). LMR was defined as the count of lymphocytes over monocytes, NLR as neutrophils over lymphocytes, and PLR as platelets over lymphocytes.

We defined overall survival (OS) as the time from the pathologic diagnosis of ESCC to the last follow-up or death. Survival rates were estimated using the Kaplan-Meier method. The log-rank test and Cox proportional-hazards model were used for univariate and multivariate analyses, respectively. Differences in categorical variables were verified using Pearson's chi-square test or Fisher's exact test. Continuous variables, including RT dose, LMR, NLR, and PLR, were divided into two groups using the maximally selected rank method. We selected cutoff values that best separated OS. A p-value of <0.05 was considered statistically significant. We used R 3.6.2 (R Development Core Team, Vienna, Austria) for the statistical analysis (11).

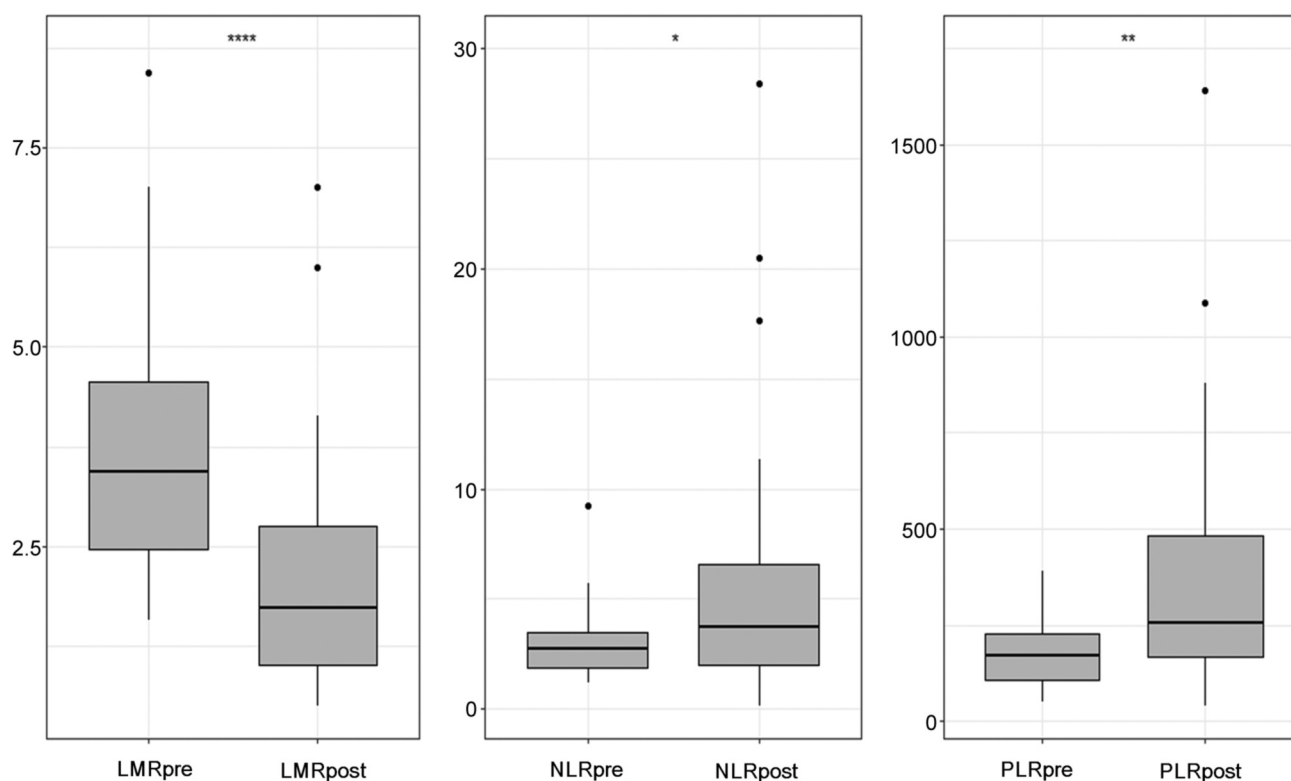


Figure 1. Box plots for lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). The middle horizontal lines indicate the median values, and the upper and lower lines of the box indicate the 75th and 25th percentiles, respectively (* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, and **** $p \leq 0.0001$).

We categorized adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Acute and chronic adverse effects were defined as adverse effects within 3 months and 4 months after the completion of dCCRT, respectively.

Results

Patients and treatments. The median age was 66 years (range=47-84 years). The location of the primary tumor was upper thoracic in 16 (24%), middle thoracic in 34 (50%), and lower thoracic in 18 (26%) patients. RT was performed using three-dimensional conformal RT (58 patients, 85%) or intensity-modulated RT (10 patients, 15%). The median total dose was 55.8 Gy (range=50-70 Gy) and the median daily dose was 1.8 Gy (range=1.8-2 Gy). The median biologically effective dose (BED) was 65.8 Gy (range=59.5-84 Gy) with $\alpha/\beta=10$. Concurrent with RT, a combination of 5-fluorouracil (5-FU) and cisplatin was administered in 63 patients (93%). On the other hand, 5-FU alone was administered in 4 patients and cisplatin alone was administered in 1 patient. After the completion of RT, 54 patients (79%) underwent adjuvant chemotherapy with a combination of 5-FU and cisplatin. Details of patient characteristics and treatment are listed in Table I.

LMR, NLR, and PLR. Before RT, the median absolute count of lymphocytes was 1,538 (range=400-3,178), monocytes 444 (range=41-1,087), neutrophils 3,710 (range=1,536-10,552), and platelets 254,500 (range=100,000-476,000). After RT, the median absolute count of lymphocytes was 600 (range=30-2,600), monocytes 400 (range=11-1,101), neutrophils 2,936 (range=54-10,040), and platelets 196,000 (range=43,000-657,000).

LMR, NLR, and PLR showed significant changes through RT (Figure 1). Before RT, the median ratio was LMR 3.64 (range=1.14-13.80), NLR 2.58 (range=1.13-13.30), and PLR 163.2 (range=50.8-647.5). After RT, the median ratio was LMR 1.35 (range=0.33-7.00), NLR 4.77 (range=0.15-52.26), and PLR 330.7 (range=39.6-6666.7). The cut-off values calculated before the start of RT were 5.75 for LMR (LMRpre), 2.50 for NLR (NLRpre), and 83.1 for PLR (PLRpre). The cutoff values calculated after the completion of RT were 2.51 for LMR (LMRpost), 5.44 for NLR (NLRpost), and 372.2 for PLR (PLRpost).

Survival outcomes and prognostic/predictive factors. The median follow-up time was 11.4 months (range=2.1-108.8 months) and the median OS was 11.4 months. The OS rates

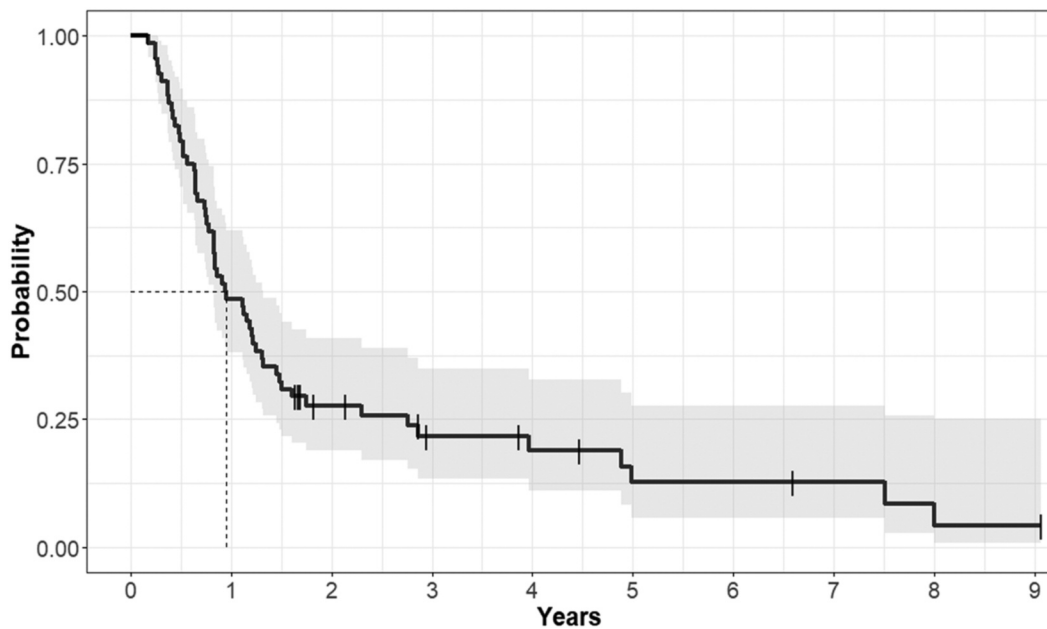


Figure 2. Overall survival curve of the entire patient population.

Table II. Multivariate analysis

Variables	Hazard ratio	(95% Confidence interval)	p-Value
Age <65 years	1.946	(1.069-3.542)	0.029
T3-4	-	-	NS
N2-3	2.421	(1.374-4.265)	0.002
High LMRpre	0.305	(0.090-1.037)	0.057
High NLRpre	1.632	(0.903-2.948)	0.105
High LMRpost	-	-	NS
High NLRpost	1.818	(1.043-3.168)	0.035
High PLRpost	-	-	NS

LMR: Lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

at 1 year and 3 years were 48.5% and 21.6%, respectively (Figure 2). In the univariate analysis, older age, higher T stage, higher N stage, higher NLRpre, lower LMRpre, higher PLRpost, higher NLRpost, and lower LMRpost were associated with poorer OS. Among the treatment factors, adjuvant chemotherapy showed improved OS in the univariate analysis, but a higher RT dose did not (Table I). We performed multivariate analyses for all the factors, except for the treatment factors. Finally, age, N stage, and NLRpost were confirmed as prognostic factors for OS (Table II, Figure 3A).

We classified patients into four groups according to the NLRpost and adjuvant chemotherapy, and then, confirmed

significant differences (Figure 3B). Patients with lower NLRpost had better OS when adjuvant chemotherapy was administered. The median OS was 16.6 *versus* 4.8 months ($p < 0.001$) for lower NLRpost with adjuvant chemotherapy and lower NLRpost without adjuvant chemotherapy, respectively. In patients with higher NLRpost, the median OS was 12.4 with adjuvant chemotherapy and 4.5 months without adjuvant chemotherapy ($p = 0.038$). The improvement in OS was remarkable in patients with lower NLRpost and adjuvant chemotherapy.

Adverse effect. Lymphopenia was the most common and most severe hematologic adverse effect recorded after dCCRT wherein it was grade 2 in 19 patients (28%), grade 3 in 18 (26%), and grade 4 in 8 (12%). Grade 2 anemia occurred in 19 patients (28%) and grade 3 in 1 (1%). Regarding neutropenia, 3 patients (4%) experienced Grade 2, 2 (3%) experienced Grade 3, and 3 (4%) experienced Grade 4. Lastly, grade 2 and 3 thrombocytopenia were both recorded in just 1 patient each (1%).

Discussion

Inflammation and cancer are closely related; inflammatory TME promotes the proliferation and survival of malignant cells as well as angiogenesis and metastasis (2, 12). Testing leukocytes obtained from peripheral blood is a cost-effective and easy-to-use method to examine the systemic status of immune and inflammatory responses.

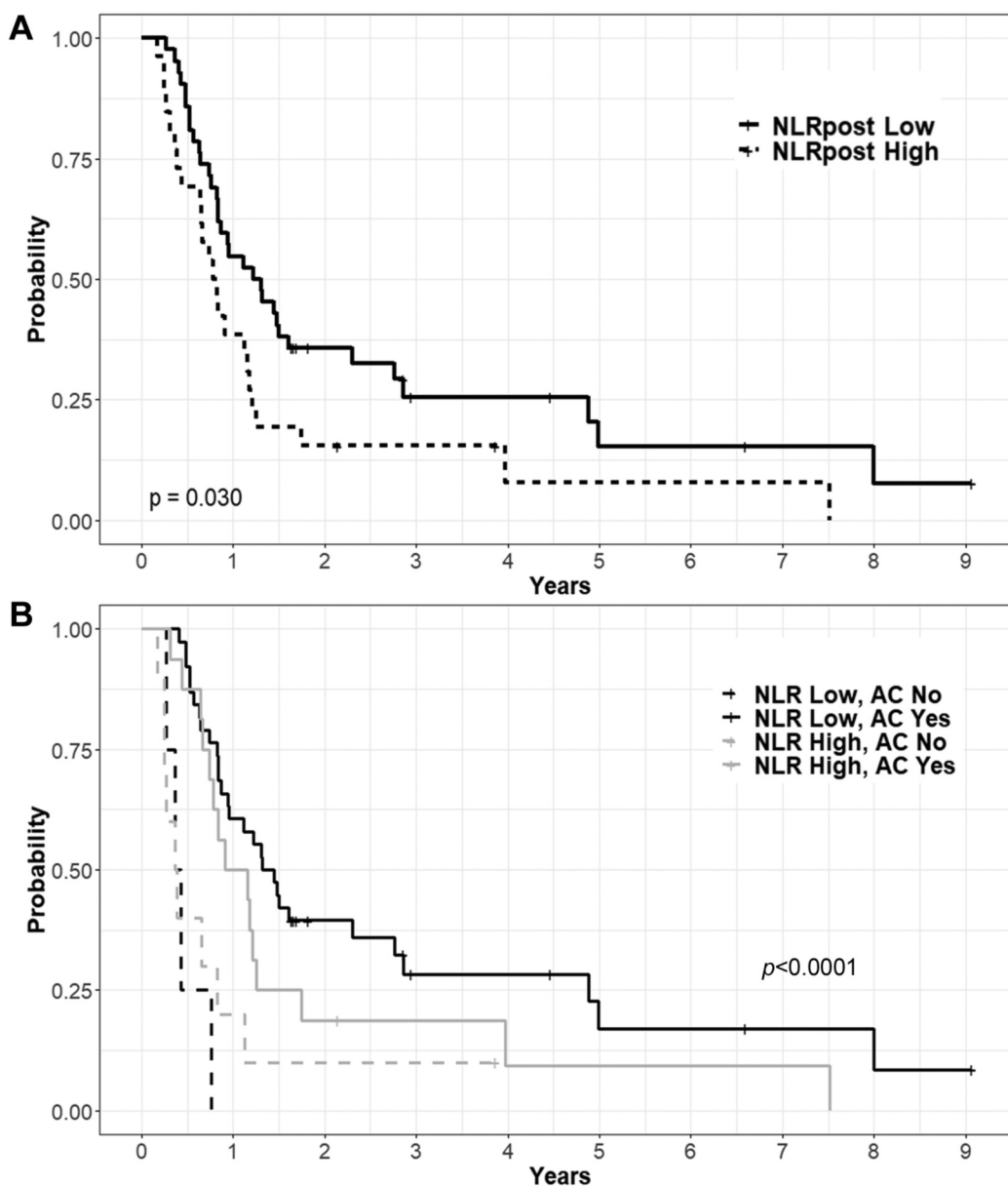


Figure 3. Overall survival curves according to the level of neutrophil-to-lymphocyte ratio (A) and adjuvant chemotherapy (B) after definitive concurrent chemoradiotherapy.

Among the peripheral blood cells, the main component of the anti-cancer immune response is the lymphocyte. Cytotoxic lymphocytes directly eradicate cancer cells *via* the death ligand/death receptor system and granular exocytosis (13). The presence of tumor-infiltrating lymphocytes, which can hinder tumor progression, is correlated with a good prognosis (14). In contrast, lymphopenia is associated with poor prognosis in solid and hematologic malignancies (15).

Neutrophils, monocytes, and platelets are also important elements of the anti-cancer immune response. In addition, neutrophils produce many kinds of pro-tumoral mediators,

such as reactive oxygen species, elastase, integrins, angiogenic factors, and proteinases. Thus, neutrophils play an important role in genetic instability, tumor cell proliferation, angiogenesis, and metastasis (16, 17). Monocytes differentiate into macrophages and migrate into the tumor tissue. As tumor-associated macrophages, monocytes ultimately participate in tumor progression by immune regulation, angiogenesis, and tumor invasion (18). Platelets are correlated with tumor metastasis. Tumor cells can induce platelet aggregation by which platelet-associated angiogenesis-regulating factors are secreted (19).

The absolute count of immune-inflammatory cells, which is affected by the myelosuppressive effect of chemotherapy (9), radiosensitivity of immune cells (8), and malnutrition due to the gastrointestinal adverse effects of dCCRT (20), should be cautiously interpreted. The absolute count of each cell shows a wide variation between patients, and changes with time even in a single patient. In contrast, relative stability could be expected when we use the ratio of immune-inflammatory cell counts, such as LMR, NLR, and PLR.

The prognostic value of the ratio of immune-inflammatory cell counts was examined in a pre-treatment setting rather than in a post-treatment setting. In this context, we compared LMR, NLR, and PLR in ESCC patients before and after dCCRT. We found that NLRpost predicts OS better than the others. As the absolute number of lymphocytes and neutrophils decreased after dCCRT, the higher NLRpost suggests that lymphocytes were affected relatively more than neutrophils. The anti-tumor activity of lymphocytes and the pro-tumor activity of neutrophils might accord with our results. To the best of our knowledge, this is the first study to evaluate the association of NLRpost and OS in ESCC patients who underwent dCCRT.

Inflammation induced by dCCRT has a yin-yang effect that can stimulate the rebound of residual malignant cells or improve therapeutic outcomes (12). NLRpost could be a good surrogate representing immune-inflammatory responses against malignant cells after the completion of dCCRT. The association between elevated NLRpost and poor survival has been reported in brain (21), head and neck (6, 22), breast (23), lung (24), and rectal (25) cancers. NLRpost has a potential benefit compared with NLRpre, which might be used to select patients who need additional therapy or intensive follow-up.

Sherry *et al.* (23) analyzed treatment outcomes of patients with stage II-III triple-negative breast cancer. NLR was calculated after the completion of RT following chemotherapy and breast surgery, and showed significant associations with locoregional failure and OS. Interestingly, among stage III breast cancer patients, patients with NLR ≥ 3 experienced a higher rate of locoregional failure than those with NLR < 3 . Since hormone therapy is limited in triple-negative breast cancer patients, close monitoring of patients using post-treatment NLR might be helpful.

In ESCC patients, several studies reported survival benefit in the addition of chemotherapy to dCCRT (10, 26, 27). However, adjuvant chemotherapy following dCCRT would not be administered to all ESCC patients considering the incidence of severe adverse effects (28, 29). Our study might contribute to the evaluation of the additional treatment group, since the benefit from adjuvant chemotherapy was notable in patients with NLRpost ≤ 5.44 (Figure 2).

A limitation of the present study is the absence of serial laboratory data during the course of dCCRT. This potentially resulted from the retrospective study design of various

institutions. The correlation between NLR dynamics and prognosis could be an independent theme for prospective studies. In addition, the functional classification of immune and inflammatory cells is becoming more sophisticated with the development of molecular biology. A future direction should be a collaborative system using NLR and molecular subtypes. Lastly, unsettled consensus of cutoff values of NLRpost is an important hurdle for clinical application.

Conclusion

We confirmed that NLRpost could be used for the prediction of prognosis in patients with ESCC who underwent dCCRT. A lower NLRpost score (≤ 5.44) was associated with better OS. In addition, NLRpost might play a role in establishing an adjuvant therapy plan following dCCRT, given that the improvement in OS was remarkable in patients with lower NLRpost and who underwent adjuvant chemotherapy.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

TK designed this study. HKK, YP, and TK collected and analyzed data. HJP, MYL, ARC, SH, and HB participated in the interpretation of results. HKK and YP drafted the article, and TK revised the article. All Authors read and approved the article.

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