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Neutrophil-to-Lymphocyte Ratio as a Predictor of Postoperative Recurrence and Prognosis in Oesophageal Squamous Cell Carcinoma

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Abstract. *Background: Trimodal therapy is frequently used for patients with locally advanced, resectable oesophageal cancer. However, it does not provide a satisfactory prognosis. The neutrophil-to-lymphocyte ratio (NLR) is an important indicator of patients' inflammatory and immune statuses. We investigated the prognostic role of NLR values obtained at different treatment stages in patients with oesophageal squamous cell carcinoma. Patients and Methods: We evaluated the correlation between NLR values or their change and prognosis at each treatment point (before chemoradiotherapy; before surgery; and at 14 days, and 1 and 2 months postoperatively) in 163 patients with oesophageal squamous cell carcinoma who underwent oesophagectomy after neoadjuvant chemoradiotherapy from April 2003 to August 2018. The outcomes studied were overall (OS) and relapse-free (RFS) survival. Results: The NLR at 1 month postoperatively showed the strongest correlation with prognosis, with an optimal cut-off value of 4.5 (area under the curve=0.7878; 95% confidence interval=0.70-0.85; p<0.0001). Univariate and multivariate analyses showed that NLR ≥4.5 was a significant factor for both RFS (hazard ratio=4.44, 95% confidence interval=2.69-7.34) and OS (hazard ratio=3.88, 95% confidence interval=2.38-6.32). Furthermore, NLR significantly stratified patients for the RFS and OS regardless of the pathological response (complete/non-complete response) and postoperative complications (Clavien–Dindo grade <IIIa/≥ IIIa). Conclusion: NLR measurement at 1 month postoperatively correlated with prognosis and was also a useful predictor of recurrence. Patients with high NLRs need more rigorous follow-up as they constitute a high-risk group. Postoperative adjuvant therapy may also be considered for such patients.*

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Key Words: Neutrophil-to-lymphocyte ratio, oesophageal squamous cell carcinoma, trimodal therapy, prognosis.

Trimodal therapy, comprising neoadjuvant chemoradiotherapy (NCRT) followed by surgery, is frequently administered for local control and to improve the survival rate of patients with locally advanced, resectable oesophageal cancer (EC). Although the survival rates of patients with EC have been improved by multidisciplinary treatment, some patients still experience early postoperative recurrence and cancer-related death even after treatment with NCRT and surgery. The reported 5-year survival rate is 40-60% for patients with locally advanced EC after trimodal therapy, and the prognosis is not good (1-3).

Whether postoperative recurrence can be reduced with EC treatment remains a major issue. With the recent development of immune checkpoint inhibitors, the therapeutic strategy for EC has dramatically changed, and further enhancement of adjuvant therapy and improvement in prognosis are expected (4). Hence, it is important to evaluate the treatment response and immune status of individual patients because they may provide information on suitable targets for intensified adjuvant therapy.

The neutrophil-to-lymphocyte ratio (NLR) is an important indicator of a patient's inflammatory and immune statuses (5-7). A change in NLR may reflect broader changes in the tumour microenvironment, and an elevated NLR in association with many solid tumours has been correlated with reduced survival (8, 9). Several studies have been conducted on evaluation of the preoperative NLR. In contrast, there are few reports on its evaluation after surgery (10). A patient's immune status and cancer progression change over time and with therapeutic intervention. Pre- and perioperative evaluation of NLR as an assessment of treatment responsiveness is a useful

Table I. *Clinicopathologic features of patients (N=163).*

Parameter		Value
Age, years	Mean±SD	63.4±7.9
Gender, n (%)	Male	137 (84.0%)
	Female	26 (16.0%)
Performance status, n (%)	0	140 (85.9%)
	1	23 (14.1%)
Tumour markers (mean±SD), ng/ml	SCC	1.9±2.1
	CEA	2.7±2.0
Primary tumour location, n (%)	Upper	34 (20.8%)
	Middle	80 (49.1%)
	Lower	49 (30.1%)
Clinical T-stage, n (%)[a]	cT1	2 (1.2%)
	cT2	20 (12.3%)
	cT3	134 (82.2%)
	cT4	7 (4.3%)
Clinical N-stage, n (%)[a]	cN0	37 (22.7%)
	cN1	94 (57.7%)
	cN2	30 (18.4%)
	cN3	2 (1.2%)
Clinical M-stage, n (%)[a]*	cM0	143 (87.7%)
	cM1	20 (12.3%)
Clinical stage, n (%)[a]	II	41 (25.2%)
	III	97 (59.5%)
	IVA	5 (3.1%)
	IVB	20 (12.2%)
	IVB	20 (12.2%)
	Complete	35 (21.4%)
Clinical response (to NCRT), n (%)[b]	Partial	122 (74.9%)
	Stable disease	5 (3.1%)
	Progressive disease	1 (0.6%)
Histology, n (%)	Well-differentiated	18 (11.0%)
	Moderately differentiated	74 (45.4%)
	Poorly differentiated	71 (43.6%)
Lymphatic invasion, n (%)	ly0	121 (74.2%)
	ly1	30 (18.4%)
	ly2	9 (5.5%)
	ly3	3 (1.9%)
Venous invasion, n (%)	v0	131 (80.4%)
	v1	29 (17.8%)
	v2	3 (1.8%)
Pathological T-stage, n (%)[c]	pT0	60 (36.8%)
	pT1	16 (9.8%)
	pT2	30 (18.4%)
	pT3	55 (33.8%)
	pT4	2 (1.2%)
Pathological N-stage, n (%)[c]	pN0	126 (77.3%)
	pN1	26 (16.0%)
	pN2	9 (5.5%)
	pN3	2 (1.2%)
Pathological M-stage, n (%)[c]	pM0	155 (95.1%)
	pM1	8 (4.9%)
Pathological response, n (%)[c]	Complete	54 (33.1%)
	Partial	109 (66.9%)
Postoperative complications, n (%)[d]	None	50 (30.6%)
	Grade I	6 (3.7%)
	Grade II	31 (19.1%)
	Grade IIIa	50 (30.7%)
	Grade IIIb	19 (11.6%)
	Grade IVa	5 (3.1%)
	Grade IVb	0
	Grade V	2 (1.2%)

CEA: Carcinoembryonic antigen; SCC: squamous cell carcinoma-related antigen; SD: standard deviation. [a]Pretherapeutic, according to TNM classification, eighth edition (11); [b]according to Response Evaluation Criteria in Solid Tumours criteria (12); [c]according to TNM classification, eighth edition (11); [d]according to Clavien–Dindo classification of surgical complications (13). *Supraclavicular lymph node metastasis.

index of recurrence and prognosis, and may provide important clues when considering indications for additional treatment in the future. The present study aimed to investigate the prognostic role of NLR values obtained at different treatment stages in patients with oesophageal squamous cell carcinoma.

Patients and Methods

Patients. This retrospective study enrolled 163 patients with oesophageal squamous cell carcinoma who underwent oesophagectomy with R0 resection after NCRT between April 2003 and August 2018 at Hiroshima University Hospital. Clinicopathological diagnosis of the tumours was performed based on the eighth edition of the TNM classification (11). Table I shows the clinicopathological features of the patients. Clinical tumour responses between pre-NCRT and restaging examinations before surgery were assessed according to the Response Evaluation Criteria in Solid Tumours criteria (12). Postoperative complications were assessed based on the Clavien–Dindo classification. Severe postoperative complications were defined as those classified as Clavien–Dindo grade IIIa or higher that developed within 30 days of surgery (13). This study was approved by the Institutional Review Board of Hiroshima University (approval number: E-2225). Informed consent was obtained from all patients for the data collected in the study.

Neoadjuvant chemoradiotherapy. NCRT comprised concurrent radiotherapy (40 Gy in 20 fractions) and chemotherapy with 5-fluorouracil and docetaxel, cisplatin, or a combination of both (14-21). Patients with elevated serum creatinine level were treated with nedaplatin instead of cisplatin. The chemotherapy regimens were docetaxel/5-fluorouracil, cisplatin/5-fluorouracil, docetaxel/cisplatin/5-fluorouracil, and nedaplatin/5-fluorouracil in 38 (23.2%), 102 (62.6%), 18 (11.0%), and 5 (3.2%) patients, respectively.

External beam radiotherapy with 10-MV X-rays was concurrently administered at 5 fractions per week for 4 weeks (total dose, 40 Gy). A computed tomography simulator was used in the three-dimensional treatment planning. The irradiation field for upper thoracic tumours included the regions from the supraclavicular, cervical, and mediastinal lymph nodes to the carina. The mid-thoracic or lower thoracic tumours field included the cervical, mediastinal, and perigastric lymph nodes; the supraclavicular fossa was included when the cervical lymph nodes tested positive. The fields for oesophagogastric junction tumours included the mediastinal (lower than the subcarinal), perigastric, and celiac lymph nodes (18-20).

Surgical treatment. Surgery was scheduled 4-8 weeks after the completion of NCRT for all patients. All patients underwent open transthoracic (n=128) or thoracoscopic oesophagectomy (n=35) and lymph node dissection in at least two fields (thoracic and abdominal fields). EC in the upper and middle third of the thoracic oesophagus and lymph node metastasis in the superior mediastinum were treated using cervical lymphadenectomy. A gastric tube was subsequently lifted for cervical anastomosis with the oesophagus. The reconstruction path was the retrosternal (n=104) or posterior mediastinal (n=57) region or the region before the chest wall (n=2). Three experts in oesophageal surgery performed these procedures.

Neutrophil-to-lymphocyte ratio. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The NLR was calculated at five points: Prior to chemoradiotherapy (pre CRT); presurgery; and 14 days (POD 14), 1 month (POM 1), and 2 months (POM 2) postoperatively. To evaluate the change in NLR due to CRT and surgery, the following parameters were also evaluated:

i) ΔNLR (CRT) = (NLR presurgery − pre-CRT NLR)
ii) ΔNLR (POD 14)=(NLR 14 days after surgery − NLR presurgery)
iii) ΔNLR (POM 1)=(NLR 1 month after surgery − NLR presurgery)
iv) ΔNLR (POM 2)=(NLR 2 months after surgery − NLR presurgery)

Table II. *Neutrophil, lymphocyte, and neutrophil-to-lymphocyte ratio (NLR) data for each treatment period in the study (N=163).*

Time point	Parameter	Value
Pre-CRT	Neutrophil count, n/μl	4,724.1±1,854.4
	Lymphocyte count, n/μl	1,710.7±607.5
	NLR	3.1±1.8
Pre-surgery	Neutrophil count, n/μl	2,863.9±1301.6
	Lymphocyte count, n/μl	999.8±447.9
	NLR	3.3±2.0
POD 14	Neutrophil count, n/μl	5,699.4±2,685.7
	Lymphocyte count, n/μl	714.4±327.2
	NLR	20.0±73.1
POM 1	Neutrophil count, n/μl	4,284.1±1,951.4
	Lymphocyte count, n/μl	883.7±427.3
	NLR	6.1±5.2
POM 2	Neutrophil count, n/μl	3,538.1±2,290.6
	Lymphocyte count, n/μl	930.2±454.8
	NLR	28.5±208.5

Values are shown as the mean±standard deviation. CRT: Chemoradiotherapy; POD: postoperative day; POM: postoperative month.

Statistical analyses. The results are presented as percentage or medians unless stated otherwise. Survival was analysed using Kaplan–Meier curves and compared using log-rank tests. Relapse-free survival (RFS) was defined as the interval between the date of surgery until the first event (recurrence or death from any cause) or the most recent follow-up. Overall survival (OS) was defined as the time from the date of surgery until death due to any cause or the last follow-up visit. Optimal cut-off values for NLR were determined from receiver operating characteristic curves. Multivariate Cox regression analysis was performed to identify the independent predictors of OS and RFS. A backward stepwise method was used to select variables for the multivariate analysis. Statistical analysis was performed using JMP Pro 15 software (2019; SAS Institute, Cary, NC, USA), with a significance level of $p<0.05$.

Results

NLR data for each treatment period. The NLR values (mean±standard deviation) were 3.1±1.8 pre CRT, 3.3±2.0 pre surgery, 20.0±73.1 at POD 14, 6.1±5.2 at POM 1, and 28.5±208.5 at POM 2 (Table II).

Optimal cut-off of the NLR at each treatment period for predicting the 3-year OS rate. The optimal cut-off values of NLR to predict good OS pre-CRT, pre-surgery, and at POD

Table III. *Results of the univariate and multivariate analyses of prognostic factors for recurrence-free survival.*

		Univariate analysis			Multivariate analysis		
Variable		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age, years	Continuous	1.01	0.97-1.02	0.8666	-		-
Gender	Female (reference)	1			1		
	Male	2.13	1.07-4.24	0.0309	1.65	0.78-3.47	0.6868
Performance status	0 (reference)	1			-	-	-
	1	1.37	0.76-2.47	0.3035	-	-	-
SCC	Continuous	0.99	0.90-1.08	0.9614	-	-	-
CEA	Continuous	1.08	0.98-1.17	0.0936	-	-	-
Primary tumour location	Middle, lower (reference)	1			-	-	-
	Upper	1.02	0.61-1.69	0.9292	-	-	-
Clinical T-stage[a]	1, 2 (reference)	1			-	-	-
	3, 4	1.62	0.84-3.13	0.1465	-	-	-
Clinical N-stage[a]	0 (reference)	1			-	-	-
	1, 2, 3	1.41	0.86-2.32	0.1673	-	-	-
Clinical M-stage[a]	0 (reference)	1			-	-	-
	1	1.60	0.90-2.83	0.1043	-	-	-
Clinical response[b]	CR, PR (reference)	1			1		
	SD, PD	3.80	1.64-8.81	0.0087	2.81	1.15-6.87	0.0233
NLR	< 4.5 (reference)	1			1		
	≥ 4.5	5.51	3.45-8.81	<0.0001	4.44	2.69-7.34	<0.0001
Pathological T-stage[c]	0, 1, 2 (reference)	1			1		
	3, 4	1.84	1.22-2.78	0.0350	1.51	0.97-2.35	0.1898
Pathological N-stage[c]	0 (reference)	1			1		
	1, 2, 3	2.64	1.74-4.00	<0.0001	1.67	1.07-2.61	0.0003
Pathological M-stage[c]	0 (reference)	1			-	-	-
	1	2.28	0.99-5.24	0.0514	-	-	-
Histology	Other (reference)	1			-	-	-
	Poorly differentiated	1.38	0.92-2.08	0.1171	-	-	-
Lymphatic invasion	0 (reference)	1			1		
	1, 2, 3	2.79	1.83-4.26	<0.0001	1.90	1.05-3.44	0.0395
Venous invasion	0 (reference)	1			1		
	1, 2	2.28	1.45-3.59	0.0004	1.20	0.64-2.26	0.7783
Postoperative complications[d]	Grade II or lower (reference)	1			-	-	-
	Grade III or higher	1.15	0.77-1.73	0.4787	-	-	-

CEA: Carcinoembryonic antigen; CI: confidence interval; CR: complete response; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PD: progressive disease; PR: partial response; RFS: relapse-free survival; SCC: squamous cell carcinoma-related antigen; SD: stable disease. [a]Pretherapeutic, according to TNM classification, eighth edition (11); [b]according to Response Evaluation Criteria in Solid Tumours criteria (12); [c]according to TNM classification, eighth edition (11); [d]according to Clavien–Dindo classification of surgical complications (13).

14, POM 1, and POM 2 were 8.1 [area under the curve=0.4822, 95% confidence interval (CI)=0.39-0.57, p=0.7861], 2.1 (AUC=0.6084, 95% CI=0.51-0.69, p=0.0196), 11.2 (AUC=0.5657, 95% CI=0.47-0.65, p=0.0075), 4.5 (AUC=0.7878, 95% CI=0.70-0.85, p<0.0001), and 3.3 (AUC=0.6041, 95% CI=0.51-0.68, p=0.0069), respectively.

For ΔNLR CRT, ΔNLR POD 14, ΔNLR POM 1, and ΔNLR POM 2, the optimal cut-off values of NLR to predict OS were 0.6 (AUC=0.5616, 95% CI=0.46-0.65, p=0.1006), 10.0 (AUC=0.5287, 95% CI=0.43-0.62, p=0.0146), 2.0 (AUC=0.6898, 95% CI=0.59-0.76, p=0.0003), and 1.4 (AUC=0.5294, 95% CI=0.43-0.61, p=0.0188), respectively.

The NLR of POM 1, which had the highest AUC, was adopted as a prognostic factor.

Univariate and multivariate analyses for RFS. Univariate analysis showed that male sex [hazard ratio (HR)=2.13, 95% CI=1.07-4.24], a poor clinical response (stable or progressive disease) (HR=3.80, 95% CI=1.64-8.81), NLR ≥4.5 (HR=5.51, 95% CI=3.45-8.81), pathological T-stage 3 or 4 (HR=1.84, 95% CI=1.22-2.78), N-stage 1-3 (HR=2.64, 95% CI=1.74-4.00), lymphatic invasion (HR=2.79, 95% CI=1.83-4.26) and venous invasion (HR=2.28, 95% CI=1.45-3.59) were significantly associated with reduced RFS (Table III).

Multivariate analysis showed that a poor clinical response (HR=3.80, 95% CI=0.13-0.37), NLR ≥4.5 (HR=0.22, 95% CI=0.13-0.37), pathological nodal metastasis (HR=1.67, 95% CI=1.07-2.61), and lymphatic invasion (HR=1.90, 95%

Table IV. *Results of the univariate and multivariate analyses of the prognostic factors for overall survival.*

Variable		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age, years	Continuous	0.99	0.97-1.02	0.8642			
Gender	Female (reference)	1			1		
	Male	2.24	1.12-4.45	0.0100	1.76	0.84-3.71	0.7759
Performance status	0 (reference)	1					
	1	1.54	0.87-2.72	0.1333			
SCC	Continuous	0.99	0.90-1.08	0.9982			
CEA	Continuous	1.07	0.97-1.16	0.1566			
Primary tumour location	Middle, lower (reference)	1					
	Upper	1.06	0.65-1.74	0.7955			
Clinical T-stage[a]	1, 2 (reference)	1					
	3, 4	1.44	0.77-2.71	0.2464			
Clinical N-stage[a]	0 (reference)	1					
	1, 2, 3	1.46	0.89-2.39	0.1303			
Clinical M-stage[a]	0 (reference)	1					
	1	1.34	0.75-2.36	0.3113			
Clinical response[b]	CR, PR (reference)	1			1		
	SD, PD	4.89	2.10-11.36	0.0002	3.83	1.54-9.49	0.0037
NLR	< 4.5 (reference)	1			1		
	≥ 4.5	5.11	3.23-8.10	<0.0001	3.88	2.38-6.32	<0.0001
Pathological T-stage[c]	0, 1, 2 (reference)	1			1		
	3, 4	2.02	1.35-3.03	0.0006	1.44	1.23-2.57	0.0247
Pathological N-stage[c]	0 (reference)	1			1		
	1, 2, 3	2.49	1.66-3.75	<0.0001	1.44	1.10-2.30	0.0008
Pathological M-stage[c]	0 (reference)	1					
	1	1.99	0.86-4.56	0.1032			
Histology	Other (reference)	1					
	Poorly differentiated	1.19	0.80-1.78	0.3759			
Lymphatic invasion	0 (reference)	1			1		
	1, 2, 3	2.59	1.71-3.91	<0.0001	1.48	0.80-2.75	0.3805
Venous invasion	0 (reference)	1			1		
	1, 2	2.36	1.52-3.67	0.0001	1.47	0.77-2.80	0.8621
Postoperative complications[d]	Grade II or lower (reference)	1					
	Grade III or higher	1.08	0.72-1.61	0.6946			

CEA: Carcinoembryonic antigen; CI: confidence interval; CR: complete response; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PD: progressive disease; PR: partial response; RFS: relapse-free survival; SCC: squamous cell carcinoma-related antigen; SD: stable disease. [a]Pretherapeutic, according to TNM classification, eighth edition (11); [b]according to Response Evaluation Criteria in Solid Tumours criteria (12); [c]according to TNM classification, eighth edition (11); [d]according to Clavien–Dindo classification of surgical complications (13).

CI=1.05-3.44) remained significantly associated with poor RFS (Table III).

Univariate and multivariate analyses for OS. Univariate analysis showed that male sex (HR=2.24, 95% CI=1.12-4.45), a poor clinical response (HR=4.89, 95% CI=2.10-11.36), NLR ≥4.5 (HR=5.11, 95% CI=3.23-8.10), high pathological T-stage (HR=2.02, 95% CI=1.35-3.03), lymph node metastasis (HR=2.49, 95% CI=1.66-3.75), lymphatic invasion (HR=2.59, 95% CI=1.71-3.91) and venous invasion (HR=2.36, 95% CI=1.52-3.67) were significantly associated with poor OS (Table IV).

Multivariate analysis showed that a poor clinical response (HR=3.83, 95% CI=1.54-9.49), NLR ≥4.5 (HR=3.88, 95% CI=2.38-6.32), high pathological T-stage (HR=1.44, 95% CI=1.23-2.57) and lymph node metastasis (HR=1.44, 95% CI=1.10-2.30) were significantly associated with poor OS (Table IV).

RFS and OS after NCRT. Five-year RFS (Figure 1A) and OS (Figure 1B) rates were higher in patients with low NLRs at POM 1 (<4.5) than in those with high values (≥4.5) (81.1% *vs.* 22.9% and 80.9% *vs.* 23.3%, respectively, both $p<0.0001$).

RFS and OS according to pathological response and postoperative complications. Whether patients attained pathological complete response (pCR) or not, the 5-year RFS rates (93.5% *vs.* 45.5% and 69.4% *vs.* 14.6%, respectively, $p<0.0001$) and OS rates (90.4% *vs.* 47.6% and 71.3% *vs.*

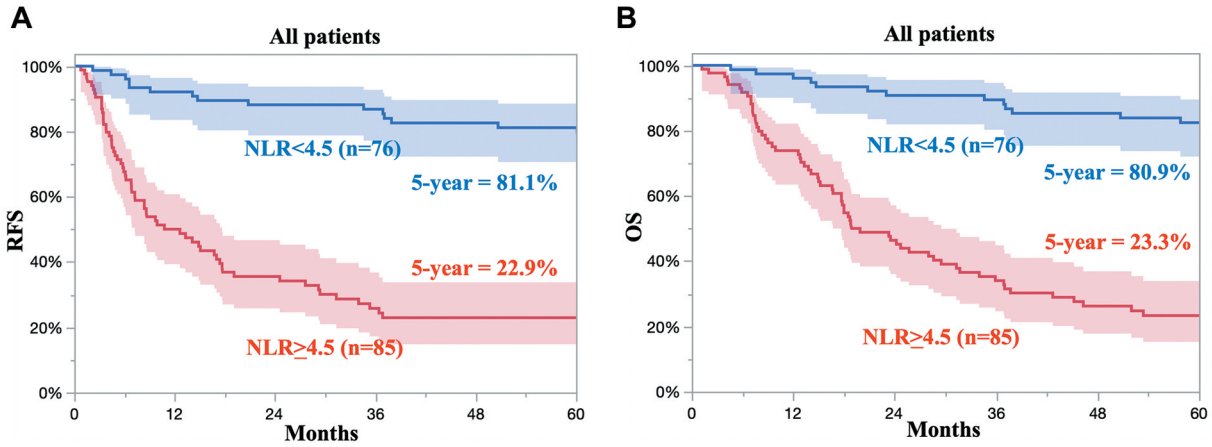

Figure 1. *Relapse-free survival (RFS) (A) and overall survival (OS) (B) after neoadjuvant chemoradiotherapy in all patients, based on the neutrophil-to-lymphocyte ratio (NLR).*

13.1%, respectively, $p<0.0001$) were higher in patients with a low NLR (<4.5) at POM 1 than in those with high values (Figure 2A and B).

Whether patients had no or only mild postoperative complications or severe ones, the 5-year RFS rates (79.7% *vs.* 24.7% and 79.6% *vs.* 22.0%, respectively, $p<0.0001$) and OS rates (82.3% *vs.* 23.7% and 79.4% *vs.* 23.5%, respectively, $p<0.0001$) were higher with a low NLR (<4.5) at POM 1 than in those with high values (Figure 2C and D).

Discussion

Lymphocytes play a role in tumour suppression and immunity and are widely used as indicators of immunocompetence (22, 23). The production of neutrophils, however, increases in response to inflammation. Neutrophils induce the production of chemokines and cytokines that enhance tumour growth, invasion, and angiogenesis; therefore, they are closely associated with inflammation and tumour progression (24). The NLR is an indicator that predicts the posthospitalization course of critically ill patients admitted to intensive care units (25); however, it has recently been reported as an oncological prognostic marker. NLR is one of the most popular methods for assessing the nutritional status of cellular components, and there is a large body of rigorous evidence supporting this methodology. It does not involve any additional costs to measure compared with other biomarkers (5-9).

The NLR is often reported as a risk factor for prognosis and recurrence (5-10), but it is useful in predicting preoperative treatment effects (26) and postoperative complications (27). The NLR is also associated with the prediction of preoperative treatment efficacy in EC. There have been various reports on the timing of NLR measurements (before and after the start of preoperative treatment) and on the amount of change in the NLR with treatment (5-9, 26, 28, 29). However, data on postoperative NLR in EC are still insufficient compared with other cancer types (30, 31).

In this study, we investigated the correlation between perioperative NLR, recurrence, and prognosis in advanced resectable oesophageal squamous cell carcinoma. We hypothesized that changes in the immune status in cancer over time and the postoperative status may contribute to early recurrence, which suggests they are important as prognostic factors. Therefore, we decided to evaluate the immune status in patients with cancer before treatment and after preoperative CRT and surgery. Three time points (POD 14, POM 1, and POM 2) were adopted for measurement.

We also focused on treatment-related changes in immune status because dynamic changes in the NLR before and after surgery have been reported (10). Nonetheless inflammation (preoperative stricture, oesophagitis, and pneumonia) and postoperative surgical invasion and complications may contribute to the NLR in EC. We also hypothesized that the postoperative NLR suggests the patient's postoperative immune status, which is more important as a prognostic factor than the change in NLR value. Thus, we examined the prognostic value of the NLR and its changes at each treatment point. The NLR at POM 1 exhibited the strongest correlation with prognosis and was identified as an important prognostic factor.

In the subgroup analysis, pCR and non-pCR cases were compared. Although the prognosis of non-pCR cases is worse than that of pCR cases (8, 32), more than half of the non-pCR cases with a high NLR had recurrence within 1 year of surgery, which indicates a very poor prognosis. Even in patients with pCR, half with a high NLR had recurrence within 3 years, indicating a poor prognosis. These results suggest that patients with a high NLR should be considered for additional adjuvant therapy, even if pCR is attained; strict follow-up may be necessary.

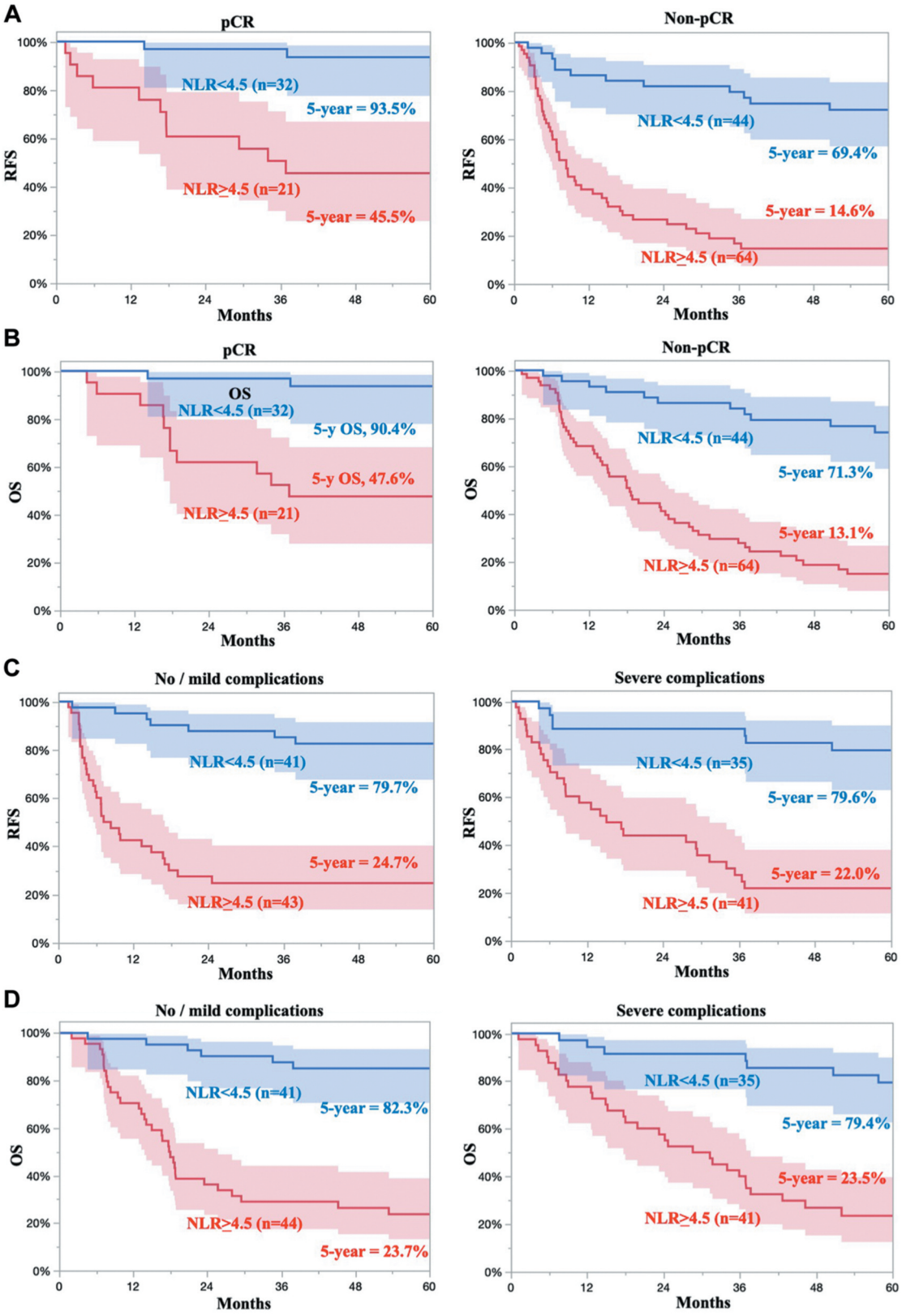

Figure 2. *Relapse-free (RFS) and overall (OS) survival after neoadjuvant chemoradiotherapy (NCRT) in patients according to the pathological response (A and B and postoperative complications (C and D), based on the neutrophil-to-lymphocyte ratio (NLR). pCR: Pathological complete response.*

Postoperative complications have been reported as a factor for poor prognosis (33, 34), and the occurrence of severe ones is likely to affect blood sampling data, including neutrophil and lymphocyte counts, after surgery. Therefore, we performed another analysis for groups with and without severe postoperative complications (Clavien–Dindo grade III or higher). Regardless of the presence of severe complications, patients with a high NLR still had a very high recurrence rate at a relatively early stage and a poor prognosis. Conversely, patients with a low NLR had a relatively good prognosis, even if they developed severe complications.

Currently, immune checkpoint inhibitors have been approved in the field of EC, and multidisciplinary treatment for EC is expected to develop further in the future (4). This study is significant as the detection of cases at high risk for postoperative recurrence and poor prognosis is useful in determining indications for additional adjuvant therapy.

This study was limited by a retrospective study design, a small number of patients, and the use of data from a single institution.

In summary, we showed that the NLR at 1 month after surgery correlated with prognosis and was also a useful predictor of recurrence. As a high-risk group, patients with a high NLR require rigorous follow-up, and postoperative adjuvant therapy should be considered for them.

Conflicts of Interest

The Authors have no related conflicts of interest to declare.

Authors' Contributions

MOh and YH drafted the article. MOh, YH, ME, YI, TK, TY, RH, and NK contributed to patient care. MOh, MK, JH, and MH performed the literature search. MOh, YH, ME, YI, TK, TY, RH, NK, and MOk participated in the critical revision of the article. All Authors read and approved the final article.

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