Preoperative neutrophil-to-lymphocyte ratio predicts the prognosis of esophageal squamous cell cancer patients undergoing minimally invasive esophagectomy after neoadjuvant…

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Manuscript title: Preoperative neutrophil-to-lymphocyte ratio predicts the prognosis of esophageal squamous cell cancer patients undergoing minimally invasive esophagectomy after neoadjuvant chemotherapy

Running head: Impact of NLR on ESCC patient survival

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Synopsis

It is important to predict prognosis of esophageal squamous cancer (ESCC) patients treated with neoadjuvant chemotherapy (NAC) followed by minimally invasive esophagectomy (MIE). Preoperative neutrophil-to-lymphocyte ratio (NLR) was independent prognostic marker for 121 ESCC patients who received NAC and MIE. In the future, NLR might contribute to introduce novel adjuvant therapy.

Abstract:

Background: One of the primary treatment for resectable advanced esophageal squamous cell cancer (ESCC) is neoadjuvant chemotherapy (NAC) followed by minimally invasive esophagectomy (MIE). Because the neutrophil-to-lymphocyte ratio (NLR) is a widely reported prognostic factor in several cancers, we investigated whether the preoperative NLR is a biomarker in ESCC patients treated with NAC and MIE.

Methods: In this study, we investigated 174 ESCC patients who underwent MIE from January 2010 to December 2015, including 121 patients who received NAC. The cutoff value of the NLR was analyzed using the receiver operating characteristic curve. Multivariate analyses were performed to clarify independent prognostic factors for overall survival (OS).

Results: The cutoff value of the NLR for OS in 121 patients who received NAC was 2.5 ng/mL, and the area under the curve was 0.63026 ($P = 0.0127$). The 5-year OS rate was 64% in those with an NLR < 2.5 and 39% in those with an NLR ≥ 2.5. According to multivariate analysis, NLR ≥ 2.5, pathological T, pathological N, and intraoperative blood loss of >415 mL were independent poor prognostic factors.

Conclusions: NLR is a biomarker of prognosis in ESCC patients who undergo MIE after NAC.

Introduction

Esophageal squamous cell cancer (ESCC) is the sixth most common cause of cancer-related deaths worldwide.[1] The number of new cases of esophageal cancer each year is estimated to be 57,000 worldwide.[2] Surgery is the preferred treatment for patients with locally advanced tumors, but esophagectomy is invasive and is associated with serious morbidity and mortality.[3, 4] Thus, minimally invasive esophagectomy (MIE) using a thoracoscopic or laparoscopic approach was developed to reduce invasiveness. [5, 6]

Particularly, esophagectomy with neoadjuvant chemotherapy (NAC) or neoadjuvant chemoradiotherapy is the predominant treatment modality.[7] Especially, NAC consisting of cisplatin (80 mg/m^2) and 5-fluorouracil (800 mg/m^2) (CF) is standard in Japan.[8] However, some patients who undergo esophagectomy and who also receive NAC still have a poor prognosis,[8] and therefore, it is important to predict which cases have a poor prognosis to initiate suitable treatment, such as other regimens, timely.

Inflammation plays an important role in carcinogenesis.[9] On the one hand, the infiltration of neutrophils seems to be a direct result of cancer cell activity, which suggests that neutrophils are associated with tumor growth.[10, 11] Alternatively, lymphocytes play an important role in tumor-specific immune responses.[12] It has also been reported that tumor infiltration by lymphocytes is associated with a better prognosis.[13] Recently, the neutrophil-to-lymphocyte ratio (NLR) has been demonstrated to be a prognostic indicator in several cancers. Calculation of the NLR is easy and inexpensive, and the data needed to determine the NLR are obtained as a result of routine clinical tests. In previous studies, a higher NLR has been known to be an indicator of a poor prognosis in colorectal cancer,[14] head and neck cancer,[15] and esophageal cancer.[16, 17] However, no reports on NLR in patients with ESCC who underwent MIE with NAC have been published. Therefore, this

study aims to clarify whether the preoperative NLR is a prognostic biomarker in patients with ESCC undergoing MIE following NAC.

MATERIALS AND METHODS

Patients and data retrieval

This study was conducted at Kobe University Hospital from January 2010 to December 2015. During this period, 220 patients with ESCC underwent McKeown MIE which is our common practice for all surgical candidates with ESCC. In this population, 22 had distant metastasis, 5 had macroscopic residual tumor, 1 underwent salvage surgery, and 18 had missing records. NAC (CF) was done for patients excluding cT1N0M0 status.[8] Finally, 174 patients were analyzed in this study. Among them, 121 patients received NAC consisting of CF. Remaining 53 patients were treated with esophagectomy alone. We calculated the NLR from the hematological data of each patient at the time of the first medical examination.

In each of the 174 cases and 121 cases treated with NAC, the cutoff value of the NLR for overall survival (OS) was calculated using the receiver operating characteristic (ROC) curve after which the patients were divided into two groups.[18, 19] We investigated the association between the NLR and the clinicopathological characteristics of the patients. In addition, we examined the independent prognostic factors for OS using the Cox proportional hazard model. Patients were also evaluated according to gender, age, tumor location, pathological T stage, pathological N stage, postoperative pneumonia, operation time, and intraoperative blood loss. TNM classification was evaluated according to the 8th edition of the Union for International Cancer Control guidelines.[20]

Complications, such as pneumonia, were evaluated according to the Clavien–Dindo classification system.[21] Finally, NLR response to treatment was evaluated whether the difference of NLR value between before and after NAC affects survival.

Statistical analysis

The cutoff value of the NLR for OS was calculated using the ROC curve. χ^2 tests were performed to evaluate the NLR and clinicopathological factors. We generated survival curves based on the NLR using the Kaplan–Meier method and compared them using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard models were performed to identify independent prognostic factors for OS.

The P value was considered significant if it was <0.05. A multivariate analysis was performed using factors for which the P value was <0.1 in the univariate analysis. All analyses were performed using JMP® 14.2 (SAS Institute Inc., Cary, NC, USA).

Receiver operating characteristic curve

ROC curve plots the sensitivity of a test versus its false-positive rate (1-specificity) for all possible cut points. The area under the ROC curve (AUC) is an indicator of test accuracy. The precise cutoff level was determined using the AUC and the highest sum values of sensitivity and specificity as indicators.[18]

RESULTS

One hundred and seventy-four patients who underwent MIE for ESCC were retrospectively analyzed. According to the ROC curve, the cutoff value of the NLR was 1.9 ng/mL (P = 0.0173; Figure 1A), and the AUC was 0.6337. One hundred seventy-four patients were divided into two groups (NLR ≥ 1.9 ng/mL; n = 118 and NLR <

1.9 ng/mL; n = 56). Table 1 shows the baseline characteristics of the 174 patients divided according to the cutoff value of the NLR. According to ROC curve, the cutoff age was 63 years, the cutoff value of operation time was 740 min, and the cutoff value of intraoperative blood loss was 415 mL for OS. We found significant relationships between NLR and pathological T stage (P = 0.0111) and blood loss (P = 0.0201).

We generated survival curves by the Kaplan–Meier method and analyzed significant differences due to NLR status using the log-rank test. Figure 1B shows that patients with an NLR < 1.9 exhibited a longer OS than patients with an NLR ≥ 1.9 (P = 0.0018). The 5-year survival rates were 77% in those with an NLR < 1.9 and 51% in those with an NLR ≥ 1.9 (Figure 1B). Univariate and multivariate analyses using the Cox proportional hazard models in 174 patients were performed to clarify the independent prognostic factors for OS. Table 2 shows that an NLR ≥ 1.9 (HR = 2.195; 95% CI: 1.103–4.367; P = 0.025), pathological T stage (P < 0.0001), pathological N stage (P < 0.0001), pneumonia (HR = 1.682; 95% CI: 1.014–2.791; P = 0.043), and operation time (HR = 1.785; 95% CI: 1.079–2.955; P = 0.024) were independent poor prognostic factors in the multivariate analysis.

Analyses were also performed in 121 patients who were treated with NAC + MIE. Figure 2A shows that the cutoff value of the NLR was 2.5 ng/mL (P = 0.0127) and that the AUC was 0.6302. These 121 patients were also divided into two groups (NLR ≥ 2.5 ng/mL; n = 61 and NLR < 2.5 ng/mL; n = 60), and the baseline characteristics of these patients are shown in Table 3. According to the ROC curve, the cutoff values of age, operation time, and intraoperative blood loss were 63 years, 711 min, and 415 mL, respectively, for OS. We found significant differences between the NLR and pathological T stage (P = 0.0118), and operation time (P = 0.0013). Figure 2B shows

that patients with an NLR < 2.5 exhibited a longer OS than patients with an NLR ≥ 2.5 (P = 0.0040). The 5-year OS rates were 64% and 39% in those with an NLR < 2.5 and NLR ≥ 2.5, respectively. Table 4 shows that an NLR ≥ 2.5 (HR = 1.922; 95% CI: 1.050–3.519; P = 0.034), pathological T stage (P = 0.029), pathological N stage (P < 0.0001), and intraoperative blood loss (P = 0.024) were independent poor prognostic factors. Concerning the affect of NLR response, there was tendency to better prognosis in NLR decreased group than in increased group without significant difference. The 5-year OS rates were 55% in NLR decreased group and 43% in NLR increased group (Figure 3).

Discussion

In this study, we attempt to define the preoperative NLR as a prognostic factor. Specifically, we demonstrated that the preoperative NLR in patients who underwent MIE plus NAC (CF) was an independent prognostic factor. Our findings are specific to patients treated with esophagectomy and NAC. Moreover, all of them underwent MIE. These are novel in comparison to previous reports.[16, 17] Without inconsistency, the cut off values of the NLR in both populations (1.9 and 2.5) correspond to past reports.[16, 17] According to a previous study of esophageal cancer, inflammation is believed to contribute to tumor progression through genetic mutations, genomic instability, and epigenetic modifications. Moreover, inflammation is also believed to stimulate angiogenesis, cause immunosuppression, promote metastasis, and participate in the formation of microenvironments where malignant cells are more likely to survive.[22, 23] Inflammatory cytokines can promote megakaryocyte proliferation, which may cause thrombocytosis and is considered a negative prognostic factor in several cancers.[24] In contrast, the role of lymphocytes in the recognition of tumor antigens provides a mechanism for a host

immune attack on cancer. It was reported that higher levels of tumor-infiltrating lymphocytes in pathological specimens were associated with a significant pathological response to NAC.[25, 26] Thus, an increase in neutrophils in inflammation and a decrease in lymphocytes lead to a poor prognosis.

The usefulness of NAC in patients with resectable ESCC has been established, but it is associated with a poor response.[8] Fluoropyrimidine and platinum doublet chemotherapy are believed to be treatments that are as acceptable as NAC for patients with resectable ESCC.[27] However, the 5-year progression-free survival rate after these treatments was shown to be <50%.[8] Although other treatments consisting of docetaxel or paclitaxel are established, they are known to be associated with hematological, gastrointestinal, and neurological toxicities[28] and to result in poor long-term survival.[29] In addition, a previous study of NAC for clinical stage II or III disease reported that the good pathological response rate of patients was 15%, and thus, most of the patients exhibit poor therapeutic responses.[30] Consequently, in some patients with ESCC, NAC is insufficient to improve prognosis.

Our results demonstrated that the depression of immune function that leads to a higher NLR would also lead to a worse prognosis after NAC. Therefore, NAC is expected to control the immune microenvironment whose NLR is elevated. Concerning the affect of NLR response to NAC, there was tendency to better prognosis in NLR decreased group than in increased group despite the fact that there was no significant difference statistically. At least, NLR status before treatment is strong prognostic factor. More large study may prove the effect of NLR response.

Today, there is an opportunity to administer immune checkpoint inhibitor therapy to patients with ESCC. Kato et al. reported that nivolumab showed continued long-term

efficacy, as seen by the stability of PFS and OS, in Japanese patients with esophageal squamous cell carcinoma.[31] Inhibitors of the immune checkpoint protein PD-1 affect the antitumor activity of T cells in that they block the binding between the PD-1 receptor and its ligands.[32] In metastatic renal cell carcinoma, NLR is reported to be one of the independent predictive factor of survival with immune checkpoint inhibitor.[33] An elevated NLR might be also helpful to introduce immune checkpoint inhibitors for ESCC if they would be introduced as neoadjuvant therapy in the near future.

This study has several limitations. First, as in all retrospective studies, there may have been potential selection bias. In addition, this study had a retrospective design and a small sample size and was conducted only at a single center. Because of these limitations, the optimal value of the NLR cutoff would be changeable. Therefore, a larger, prospective, and multicenter trial will be expected to confirm our findings.

Conclusion

Our study demonstrated that an elevated NLR is a prognostic factor in patients with ESCC treated with MIE and NAC using CF.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest or financial to disclose.

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None of the authors have anything to disclose.

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Data availability statement

Research data are not shared.

Figure legend

Figure 1A

A receiver operating characteristic curve was generated to analyze the relationship between the NLR and overall survival in 174 patients. NLR, neutrophil-to-lymphocyte ratio. P = 0.0173, AUC = 0.63777

Figure 1B

Kaplan–Meier curves that were generated to analyze the survival differences among the 174 patients divided according to the cutoff value of the NLR are shown. The patients with an NLR < 1.9 exhibited a longer overall survival than patients with an NLR ≥ 1.9 (P = 0.0018).

Figure 2A

A receiver operating characteristic curve was generated to analyze the relationship between the NLR and overall survival in 121 patients who received NAC.
P = 0.0127, AUC = 0.63026

Figure 2B

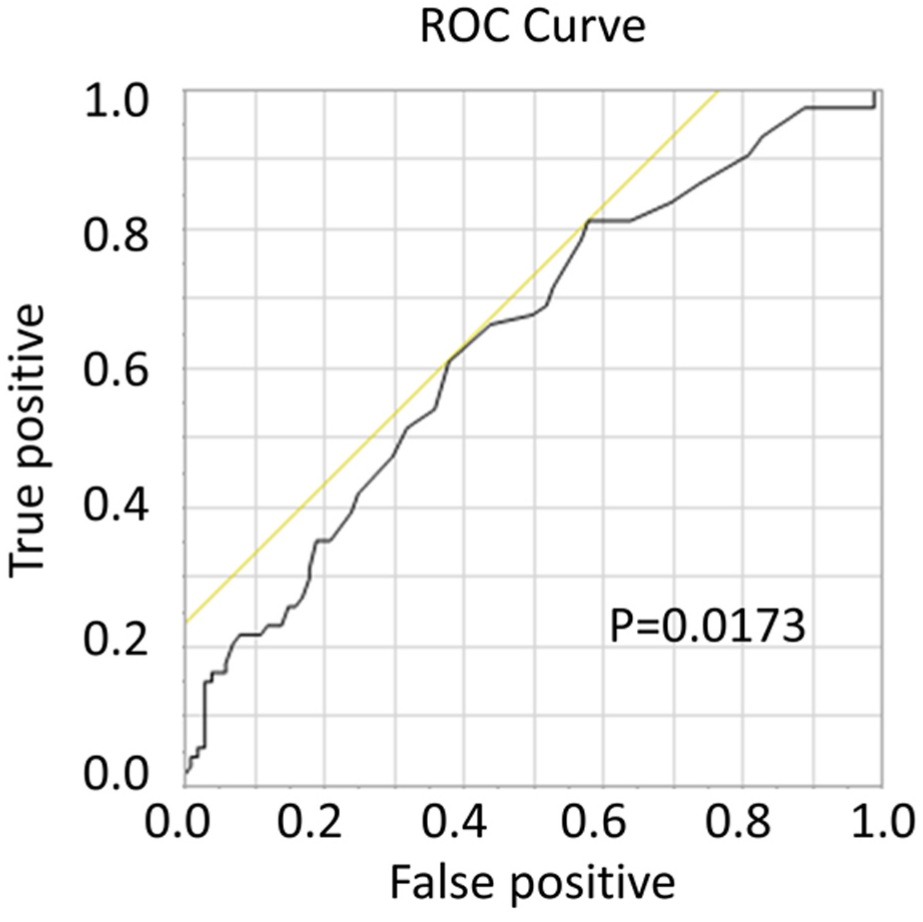
Kaplan–Meier curves were generated to analyze the survival differences among 121 patients treated with NAC who were divided according to the cutoff value of the NLR. The 5-year overall survival rate in patients with an NLR < 2.5 (64%) was significantly better than that in patients with an NLR ≥ 2.5 (39%) (P = 0.004).

Figure 3

Kaplan–Meier curves were generated to analyze the survival differences among 121 patients treated with NAC who were divided according to the NLR status. The 5-year overall survival rate in patients whose NLR decreased during NAC (55%) was not significantly better than that in patients whose NLR increased during NAC (43%) despite the fact that there was tendency to better prognosis in NLR decreased group.

Authorship

1) Substantial contributions to the conception or design of the work, or acquisition, analysis, or interpretation of data for the work: **N.Urakawa, M.Yamamoto, H.Hasegawa, K.Yamashita, and T.Matsuda.**
2) Drafting the work or revising it critically for important intellectual content: **T.Kato, and T.Oshikiri.**
3) Final approval of the version to be published: **Y.Kakeji.**
4) Agreement to be 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: **G.Takiguchi, S.Kanaji, T.Nakamura,** and **S.Suzuki.**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True positive
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0.2
0.4
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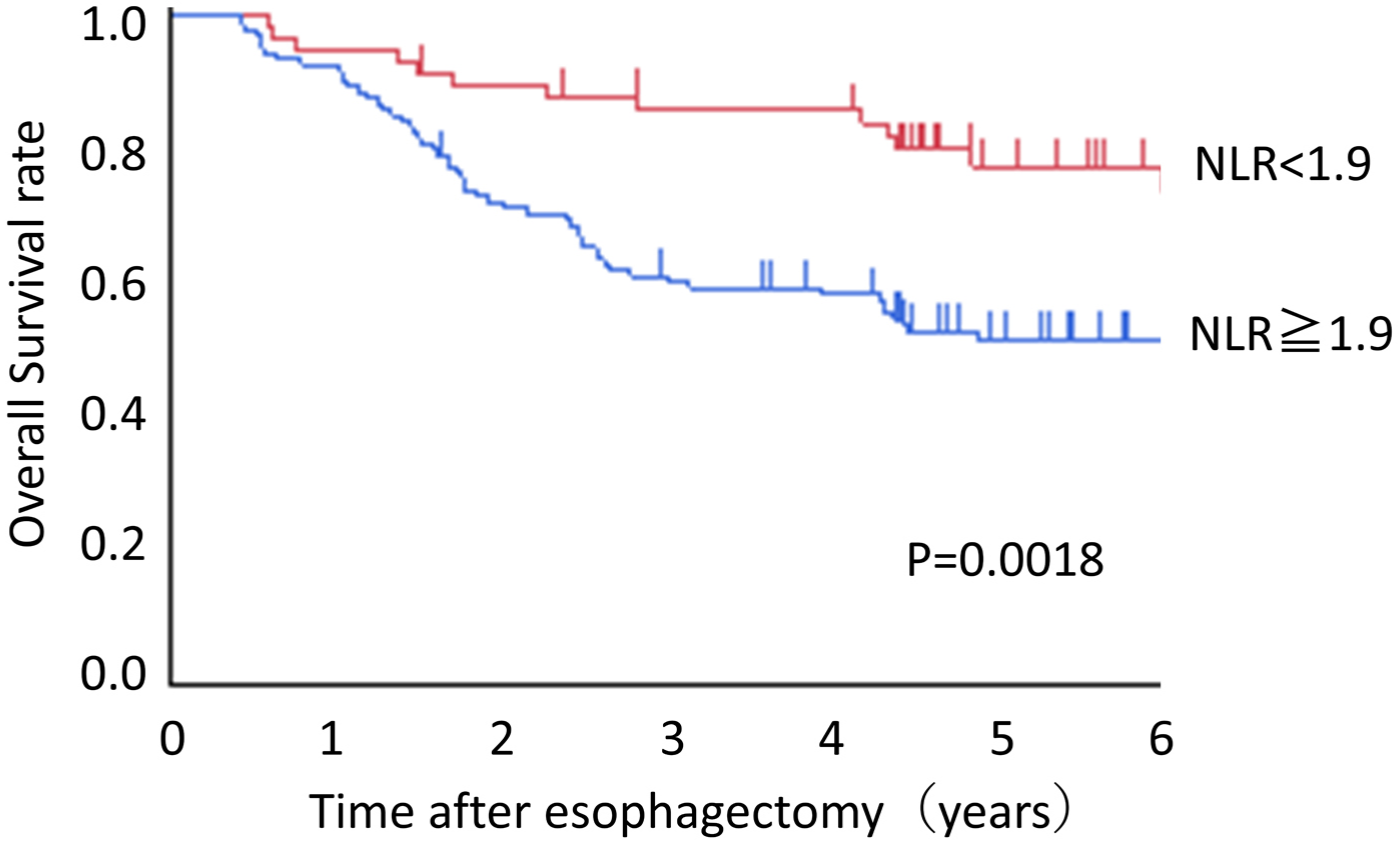
False positive
P=0.0173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Overall Survival rate
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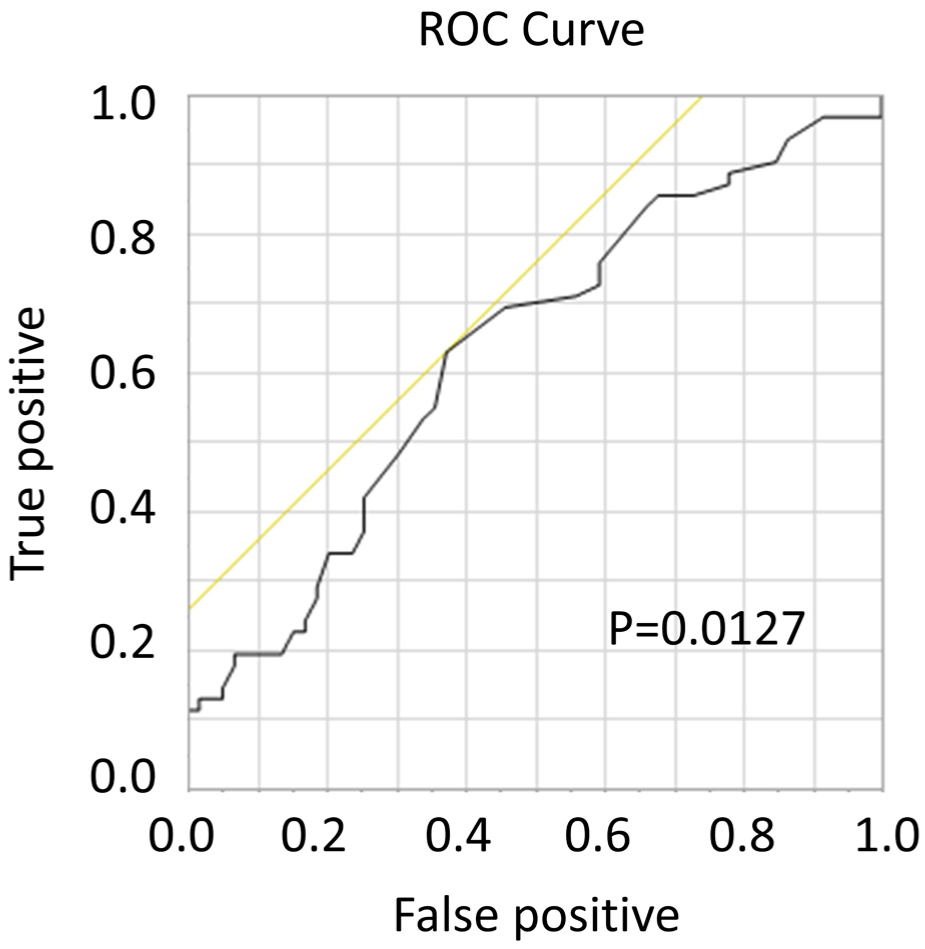
Time after esophagectomy（years）
NLR<1.9
NLR≧1.9
P=0.0018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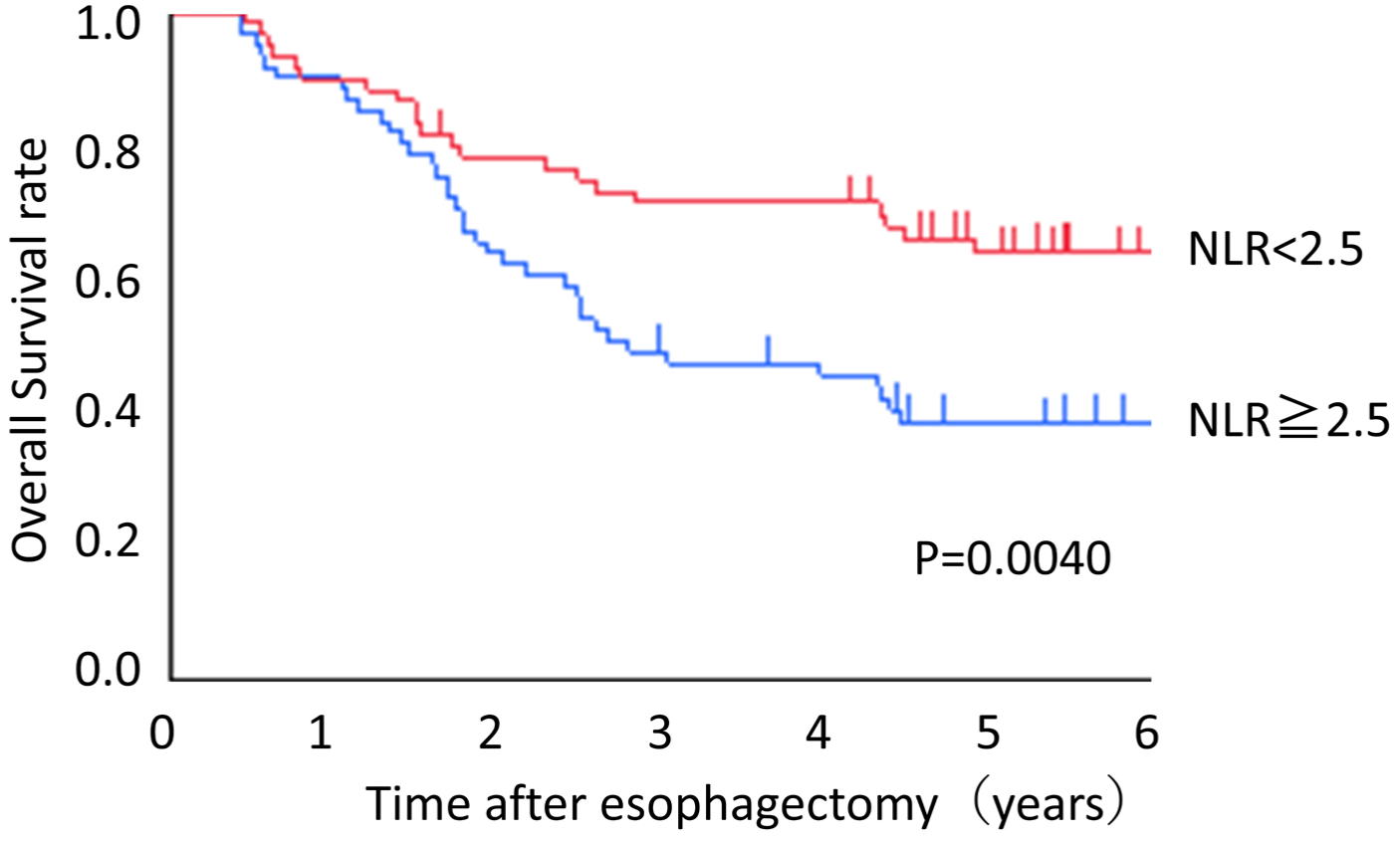
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Overall Survival rate
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Time after esophagectomy （years）
NLR<2.5
NLR≧2.5
P=0.0040

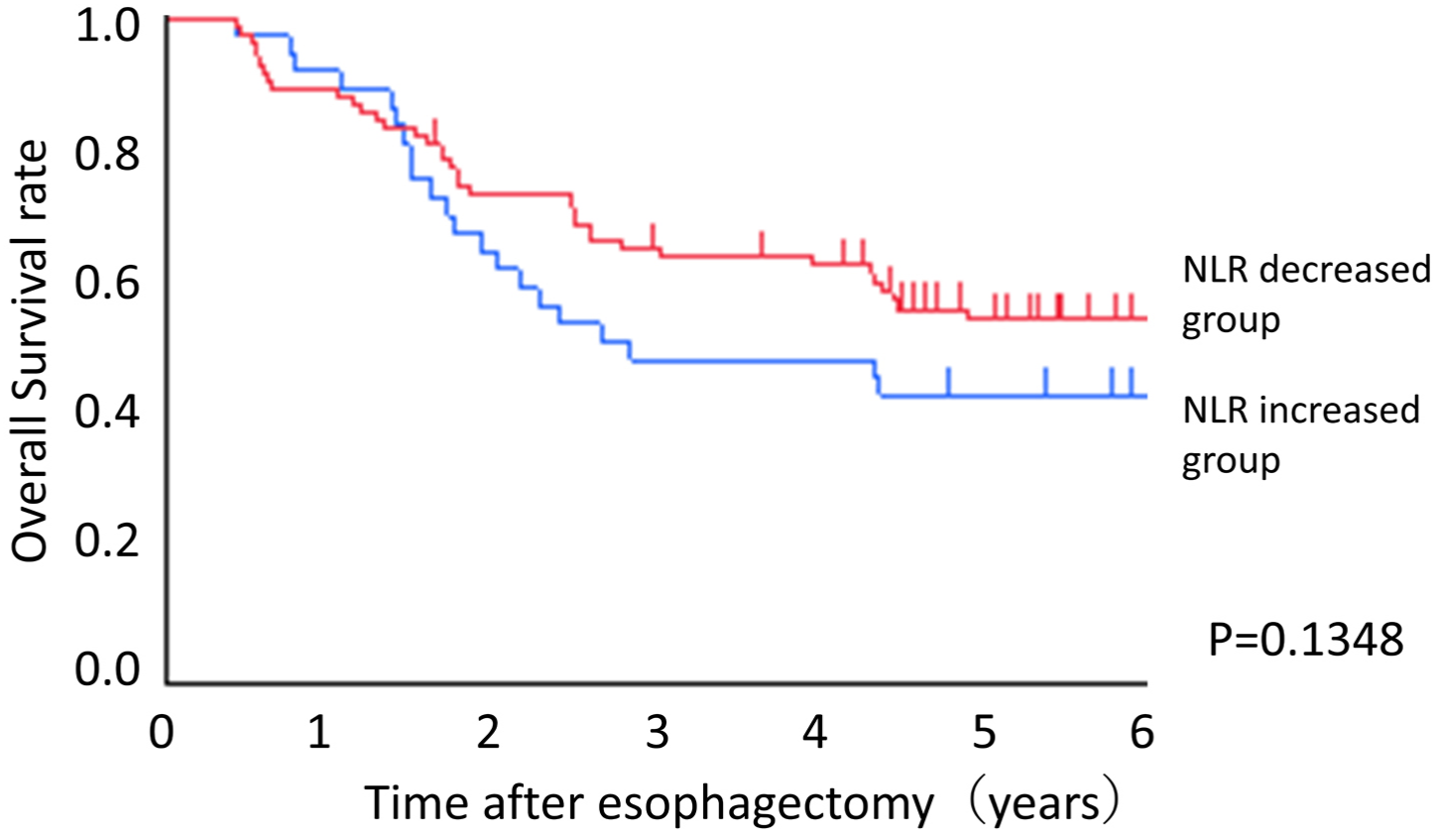
1.0
0.8
0.6
0.4
0.2
0.0
Overall Survival rate
0
1
2
3
4
5
6
Time after esophagectomy（years）
NLR decreased group
NLR increased group
P=0.1348

Table 1. Characteristics of 174 patients divided according to the cutoff point for the NLR

	Total n = 174	NLR ≥ 1.9 n = 118	NLR < 1.9 n = 56	P value
Gender				0.7758
Male/Female	154 (89%)/20 (11%)	105 (89%)/13 (11%)	49 (87%)/7 (13%)	
Age				0.1684
≥63/<63	121 (70%)/53 (30%)	86 (73%)/32 (27%)	35 (63%)/21 (37%)	
Tumor location				0.3428
Ut	30 (17%)	21 (18%)	9 (16%)	
Mt	86 (50%)	54 (46%)	32 (57%)	
Lt	58 (33%)	43 (36%)	15 (27%)	
pT Stage (8th)*				0.0111
T1	105 (60%)	62 (53%)	43 (77%)	
T2	12 (7%)	10 (8%)	2 (3%)	
T3	54 (31%)	43 (36%)	11 (20%)	
T4	3 (2%)	3 (3%)	0 (0%)	
pN Stage (8th)*				0.1019
N0	88 (51%)	55 (47%)	33 (59%)	
N1	57 (33%)	41 (35%)	16 (29%)	
N2	21 (12%)	18 (15%)	3 (5%)	
N3	8 (4%)	4 (3%)	4 (7%)	
Surgical margin				0.9331

Negative/positive	158(91%)/16(9%)	107(91%)/11(9%)	51(91%)/5(9%)	
Pneumonia**				0.0620
+/−	50 (29%)/124 (71%)	39 (33%)/79 (67%)	11 (20%)/45 (80%)	
Operation time (min)				0.1570
≥740/<740	56 (32%)/118 (68%)	42 (36%)/76 (64%)	42 (75%)/14 (25%)	
Blood loss (mL)				0.0201
≥415/<415	68 (39%)/106 (61%)	53 (45%)/65 (55%)	15 (27%)/41 (73%)	

*UICC, Union for International Cancer Control

** Higher than Clavien–Dindo classification grade II was recognized as a postoperative morbidity.

NLR, neutrophil to lymphocyte ratio

Table 2. Univariate and multivariate analyses using the Cox proportional hazard model in 174 patients to determine independent prognostic factors for overall survival

Factors	Patients (n = 174)	Overall Survival			
		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Gender					
Male/Female	154/20	1.049 (0.503–2.188)	0.897		
Age					
≥63/<63	121/53	1.403 (0.833–2.365)	0.202		
Tumor location			0.528		
Ut	30	1.000			
Mt	86	1.152 (0.598–2.220)	0.671		
Lt	58	1.432 (0.725–2.828)	0.300		
NLR					
≥1.9/<1.9	118/56	2.447 (1.367–4.382)	0.0026	2.195 (1.103–4.367)	0.025
pT Stage (8th)			<0.0001		<0.0001
T1	105	1.000		1.000	
T2	12	2.197 (0.903–5.347)	0.0826	2.031 (0.799–5.157)	0.136
T3	54	5.290 (3.184–8.790)	<0.0001	3.802 (2.169–6.661)	<0.0001
T4	3	10.784 (3.231–35.993)	0.0001	8.221 (2.204–30.660)	0.0017

pN Stage (8th)			<0.0001		<0.0001
N0	88	1.000		1.000	
N1	57	1.490 (0.850–2.613)	0.163	1.071 (0.600–1.909)	0.815
N2	21	5.742 (3.102–10.629)	<0.0001	2.687 (1.342–5.381)	0.053
N3	8	13.767 (5.833–32.492)	<0.0001	24.120 (8.444–68.897)	<0.0001
Pneumonia*					
+/−	50/124	1.497 (0.928–2.416)	0.097	1.682 (1.014–2.791)	0.043
Operation time(min)					
≥740/<740	56/118	1.935 (1.221–3.068)	0.0049	1.785 (1.079–2.955)	0.024
Blood loss(mL)					
≥415/<415	68/106	1.895 (1.199–2.995)	0.0062	1.531 (0.935–2.507)	0.090

*Higher than Clavien–Dindo classification grade II was recognized as a postoperative morbidity

HR, hazard ratio; CI, confidence interval; Lt, lower thoracic; Mt, middle thoracic; Ut, upper thoracic

Table 3. Characteristics of 121 patients who were treated with neoadjuvant chemotherapy and who were divided according to the cutoff point for the NLR

	Total n = 121 n (%)	NLR ≥ 2.5 n = 61 n (%)	NLR < 2.5 n = 60 n (%)	P value
Gender				0.5471
Male/Female	107 (88%)/14 (12%)	55 (90%)/6 (10%)	52 (87%)/8 (13%)	
Age				0.8867
≥63/<63	86 (71%)/35 (29%)	43 (70%)/18 (30%)	43 (72%)/17 (28%)	
Tumor location				0.0678
Ut	17 (14%)	11 (18%)	6 (10%)	
Mt	58 (48%)	23 (38%)	35 (58%)	
Lt	46 (38%)	27 (44%)	19 (32%)	
pT Stage (8th)*				0.0118
T1	57 (47%)	21 (34%)	36 (60%)	
T2	11 (9%)	7 (12%)	4 (7%)	
T3	50 (41%)	30 (49%)	20 (33%)	
T4	3 (3%)	3 (5%)	0 (0%)	
pN Stage (8th)*				0.2446
N0	50 (41%)	25 (41%)	25 (42%)	
N1	45 (37%)	21 (35%)	24 (40%)	

N2	19 (16%)	13 (21%)	6 (10%)	
N3	7 (6%)	2 (3%)	5 (8%)	
Surgical margin				0.9738
Negative/Positive	107(88%)/14(12%)	54(89%)/7(11%)	53(88%)/7(12%)	
Pneumonia**				0.4612
+/−	36 (30%)/85 (70%)	20 (33%)/41 (67%)	16 (27%)/44 (73%)	
Operation time(min)				0.0013
≥711/<711	56 (46%)/65 (54%)	37 (61%)/24 (39%)	19 (32%)/41 (68%)	
Blood loss(mL)				0.0781
≧415/＜415	52 (43%)/69 (57%)	31 (51%)/30 (49%)	21 (35%)/39 (65%)	

*UICC, Union for International Cancer Control

**Higher than Clavien–Dindo classification grade II was recognized as a postoperative morbidity.

Table 4. Univariate and multivariate analyses using Cox proportional hazard models to determine independent prognostic factors for overall survival (121 patients who were treated with neoadjuvant chemotherapy)

Factors	Patients (n = 121)	Overall Survival			
		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Gender					
Male/Female	107/14	1.012 (0.460–2.226)	0.975		
Age					
≥63/<63	86/35	1.623 (0.894–2.944)	0.111		
Tumor location			0.904		
Ut	17	1.000			
Mt	58	1.169 (0.554–2.467)	0.680		
Lt	46	1.174 (0.542–2.542)	0.682		
NLR					
≥2.5/<2.5	61/60	2.112 (1.255–3.556)	0.0049	1.922 (1.050–3.519)	0.034
pT Stage (8th)			<0.0001		0.029
T1	57	1.000		1.000	
T2	11	1.898 (0.752–4.792)	0.174	1.791 (0.691–4.644)	0.230
T3	50	3.767 (2.106–6.738)	<0.0001	2.430 (1.262–4.677)	0.0078
T4	3	7.912 (2.305–27.158)	0.001	5.141 (1.305–20.243)	0.0192
pN Stage (8th)			<0.0001		<0.0001

N0	50	1.000		1.000	
N1	45	1.650 (0.865–3.147)	0.128	1.572 (0.809–3.053)	0.181
N2	19	5.829 (2.880–11.797)	<0.0001	3.722 (1.687–8.213)	0.001
N3	7	38.124 (13.220–109.937)	<0.0001	42.940 (12.806–143.984)	<0.0001
Pneumonia*					
+/−	36/85	1.680 (0.997–2.830)	0.051	1.687 (0.956–2.976)	0.070
Operation time (min)					
≥711/<711	56/65	1.802 (1.089–2.982)	0.0219	1.571 (0.903–2.733)	0.109
Blood loss (mL)					
≥415/<415	52/69	1.946 (0.179–3.213)	0.0092	1.861 (1.084–3.195)	0.024

*Higher than Clavien–Dindo classification grade II was recognized as a postoperative morbidity.

HR, hazard ratio; CI, confidence interval; Lt, lower thoracic; Mt, middle thoracic; Ut, upper thoracic