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Impact of the Platelet-to-Lymphocyte Ratio as a Biomarker for Esophageal Squamous Cell Carcinoma

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Short running title: Impact of PLR as a biomarker for ESCC

Abstract

Background/Aim: Esophageal squamous cell carcinoma (ESCC) is a deadly malignant disease. This study examined whether the platelet-to-lymphocyte ratio (PLR) can be used as a biomarker to evaluate prognosis in patients with advanced ESCC following neoadjuvant chemotherapy (NAC) and undergoing minimally invasive esophagectomy (MIE).

Materials and Methods: We examined 174 patients between January 2010 and December 2015. Of these, 121 were treated with NAC. The PLR cutoff was determined through receiver-operating characteristic curve analysis. Univariate and multivariate analyses were conducted to identify prognostic factors for overall survival (OS).

Results: The PLR cutoff for OS in 121 patients was 169.6. Patients with PLR ≥ 169.6 had worse 5-year OS rates (31.1%) than those with a PLR < 169.6 (61.1%, $p = 0.001$). Multivariate analysis revealed that a PLR of ≥ 169.6 was an independent factor for poor prognosis.

Conclusion: PLR is an independent prognostic factor for patients with ESCC after NAC and MIE.

Introduction

Esophageal squamous cell carcinoma (ESCC) is the sixth leading cancer-related cause of death worldwide (1). Despite improvements in surgical techniques (2-4), treatment strategies, and postoperative care, the morbidity and mortality associated with ESCC remain serious, with 5-year overall survival (OS) rates ranging within 15%–25% (5, 6). Neoadjuvant chemotherapy (NAC) is one of the standard treatment strategies used worldwide. In Japan, 5-fluorouracil and cisplatin (FP) are typically used preoperatively in patients with advanced ESCC (7). However, esophagectomy is an invasive surgery and is thought to be a cause of high morbidity and mortality (8, 9). Minimally invasive esophagectomy (MIE), which employs both laparoscopic and thoracoscopic approaches, has become popular for downregulating invasiveness and the overall risk of postoperative respiratory complications, such as atelectasis (10-13). Furthermore, perioperative inflammatory responses play a key role in carcinogenesis (14). For instance, the neutrophil-to-lymphocyte ratio (NLR), which is a clear and immediate inflammatory marker, has been used as a prognostic biomarker in ESCC (15). In addition, the serum platelet-to-lymphocyte ratio (PLR) has been used to predict tumor behavior in several solid tumors (16-20). However, there have been no reports on PLR in ESCC patients treated with MIE after NAC. Despite platelets acting as primary agents in hemostasis (21), the interaction between tumor microenvironments and platelets controls the modulation of angiogenesis (22). Therefore, this study examines whether the preoperative PLR is a useful prognostic factor for ESCC patients treated with MIE after NAC.

Materials and Methods

McKeown MIE, which is our standardized surgical procedure, was performed between January 2010 and December 2015 in 220 patients with ESCC placed in the prone position. Among them, 22 patients with metastatic spread, five patients who underwent macroscopic incomplete resection, one patient who underwent salvage operation, and 18 patients with missing reports were excluded. In total, 174 patients with ESCC, of which 121 were treated with NAC, were enrolled. NAC comprised two 21-day courses of FP (800 mg/m² of 5-fluorouracil and 80 mg/m² of cisplatin). Esophagectomy alone was performed in the remaining 53 patients with a cT1N0M0 status. PLR was calculated from the hematological data obtained during the initial and preoperative medical examinations.

The patients were then divided into two groups according to the PLR cutoff for OS, which was calculated using receiver operating characteristic (ROC) analysis (23, 24). We assessed the relationship between the PLR values and clinicopathological factors. We then investigated the independent prognostic factors for OS using the Cox proportional hazard model. We also classified the patients according to sex, age, tumor location, tumor invasion depth, lymph node metastasis, postoperative anastomotic leakage, postoperative pneumonia, operative time, and operative blood loss. The tumor invasion depth and lymph node metastasis were evaluated using the eighth edition of the Union for International Cancer Control classification of malignant tumors (25). Perioperative complications were evaluated according to the Clavien–Dindo classification (26).

Our research was approved by the institutional review board at Kobe University.

Statistical analyses

The PLR cutoffs for OS, age, operative time, and amount of blood loss during surgery were determined using ROC curve analysis. To evaluate the relationship between PLR values and clinicopathological factors, we used the χ^2 test. Survival curves by PLR were examined using the Kaplan–Meier and log-rank tests. To identify independent prognostic factors for OS, univariate and multivariate analyses were performed using the Cox proportional hazard model. Statistical significance was set at $p < 0.1$ in the univariate analysis and $p < 0.05$ in the subsequent multivariate analysis. We used JMP® (version 14.2; SAS Institute Inc., Cary, NC, USA) for all analyses.

We used ROC curves to plot the sensitivity and false-positive rates for the cutoffs, and the area under the ROC curve (AUC) indicated the accuracy of the test (23).

Results

According to the ROC curve, the PLR cutoff for OS was 169.6 ($p = 0.0183$; Figure 1a). The patients were divided into two groups based on their PLRs (PLR ≥ 169.6 , $n = 58$; and PLR < 169.6 , $n = 116$). Table I presents the characteristics of both groups. The cutoff values for age, operative time, and intraoperative blood loss, which were determined according to the ROC curve for OS, were 63 years, 740 minutes, and 415 mL, respectively. There were no significant differences in clinicopathological factors according to PLR values (Table I). Figure 1b presents the OS curves for both groups. The OS was shorter in those with a PLR ≥ 169.6 ($p = 0.0089$). The 5-year OS rates among those with a PLR < 169.6 and those with a PLR ≥ 169.6 were 66.1% and 46.6%, respectively. As presented in Table II, multivariate analysis showed that a PLR of ≥ 169.6 (hazard ratio [HR], 1.812; 95% confidence interval [CI], 1.063–3.089; $p = 0.028$), tumor invasion depth ($p < 0.0001$), lymph node metastasis ($p < 0.0001$), pneumonia (HR,

1.791; 95% CI, 1.086–2.953; $p=0.022$), and operative time (HR, 1.819; 95% CI, 1.095–3.021; $p=0.020$) were independent prognostic factors of low OS.

We also analyzed the data of 121 patients who underwent NAC followed by MIE. As presented in Figure 2a, the PLR cutoff was also 169.6 ($p=0.0016$), and the AUC was 0.6439. The patients were also divided by PLR cutoff values (PLR ≥ 169.6 , $n=40$; and PLR < 169.6 , $n=81$). Table III illustrates the characteristics of both groups. The cutoff values for age, operative time, and perioperative blood loss, which were determined according to the ROC curve for OS, were 63 years, 711 minutes, and 415 mL, respectively. We found a significant difference in intraoperative blood loss based on PLR ($p=0.0233$). Figure 2b presents the OS curves for the two groups. The OS was shorter in those with a PLR ≥ 169.6 ($p=0.0010$). The 5-year OS rates among those with a PLR < 169.6 and those with a PLR ≥ 169.6 were 61.1% and 31.1%, respectively. As presented in Table IV, multivariate analysis showed that a PLR of ≥ 169.6 (HR, 2.350; 95% CI, 1.293–4.243; $p=0.005$), tumor invasion depth ($p=0.0161$), lymph node metastasis ($p<0.0001$), and intraoperative blood loss (HR, 1.775; 95% CI, 1.008–3.126; $p=0.046$) were independent factors of poor prognosis.

Discussion

To the best of our knowledge, this is the first study to examine preoperative PLR as a prognostic factor in patients undergoing MIE and NAC who were using FP. Our findings are specific because all patients underwent MIE. Compared to findings of previous studies that describe post-thoracostomy esophagectomy, those of our study are novel. Inflammations in living bodies, such as breast tumors, play an important role in tumor proliferation and promotion of angiogenesis and metastasis (27). In addition, inflammation may be associated with the microenvironment where malignant cell

growth is promoted (28, 29). Platelets produce various cytokines, such as vascular endothelial growth factors, which regulate angiogenesis (30, 31). Platelets, which are activated by inflammatory cells, can also promote neoplasm growth in endothelial cells (32). For example, in gastric cancer, research shows platelets promote a malignant reaction to gastric cancer cells through direct contact between the epithelium and the mesenchyme (33). Therefore, the role of platelets in tumor growth, inflammation, and regeneration has become widely recognized.

Conversely, it has been suggested since 1863 that lymphoreticular cell infiltration may contribute to carcinogenesis at chronic inflammatory sites (34). Specific tumor-infiltrating lymphocyte subsets (TILs) influence tumor growth and regression (28). The impact of TILs has generally been investigated on several digestive organ tumors (35). However, few studies have examined the relationship between TILs and the prognosis of esophageal cancers (36, 37).

Our study demonstrated that a higher PLR before NAC was related to poor immune function and poor prognosis. According to the CheckMate 577 trial, adjuvant therapy using nivolumab prolonged the disease-free survival in patients with resected gastroesophageal junctions or esophageal cancers who were treated with neoadjuvant chemoradiotherapy (38). The significance of NAC for advanced ESCC has been recognized; however, there are few effective regimens (7). Therefore, it is important to identify novel biomarkers that may respond to chemotherapy or immune checkpoint inhibitors (ICIs). Long-term results have demonstrated the efficacy of ICIs in patients with ESCC. PD-L1 tumor expression and TILs could also be useful for determining whether to introduce ICI therapy (39). Our results suggest that PLR may help predict the efficacy of NAC and ICIs. However, it is difficult to prognosticate using

a single biomarker. Further studies are required to identify biomarkers in larger populations.

This study has several limitations. First, there was potential selection bias because the patients were retrospectively analyzed. Second, the study had a small sample size and was conducted at a single center. Therefore, a larger trial size, based on a bigger dataset, is needed to confirm our findings.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Takashi Kato, Taro Oshikiri, Hironobu Goto, and Yoshihiro Kakeji designed the study. Hitoshi Harada, Naoki Urakawa, and Shingo Kanaji interpreted the study data. Ryuichiro Sawada, Hiroshi Hasegawa, Kimihiro Yamashita, and Takeru Matsuda analyzed the data. All authors revised the report, commented on the manuscript, and approved the final report.

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We confirm that this paper has not been published or contributed to other journals.

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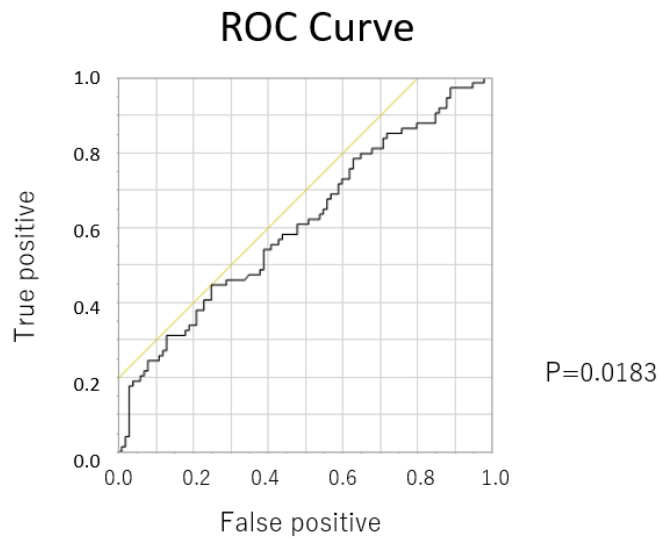


Figure 1a. To assess the correlation between the cutoff value of PLR and overall survival in 174 patients, we performed an ROC curve analysis. $p=0.0183$, AUC=0.60872. PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; AUC, area under the curve

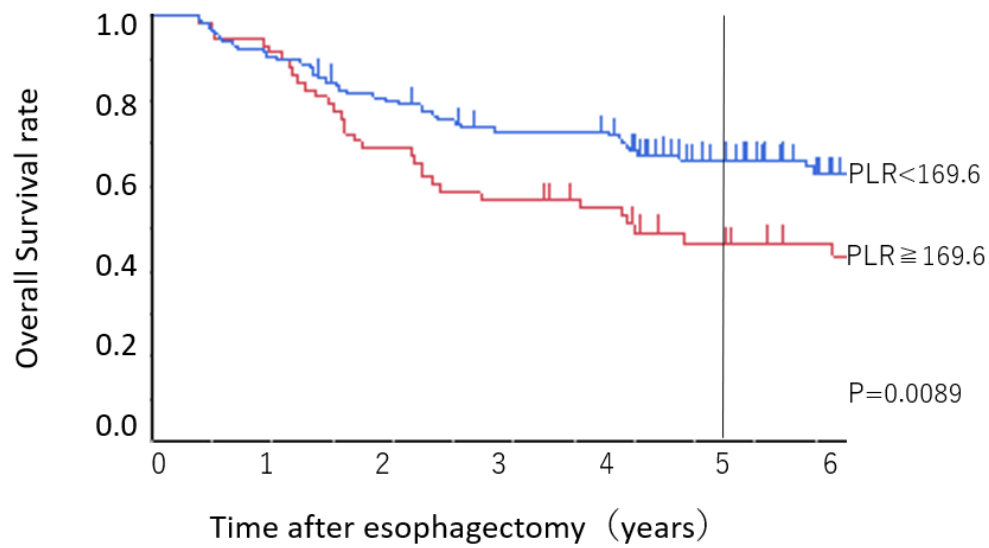


Figure 1b. Kaplan–Meier curve analysis was performed to evaluate overall survival differences in 174 patients. Patients were divided into two groups according to the PLR cutoff value of 169.6. Those with a PLR ≥ 169.6 exhibited worse overall survival than those with a PLR < 169.6 ($p = 0.0089$). PLR, platelet-to-lymphocyte ratio

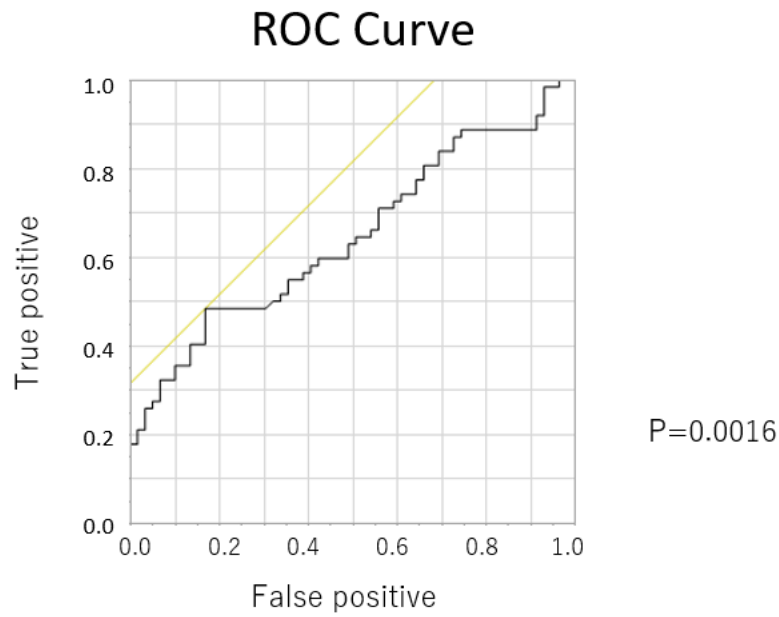


Figure 2a. To assess the correlation between the cutoff value of PLR and overall survival in 121 patients, we performed an ROC curve analysis. $p=0.0016$, $AUC=0.64393$. PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; AUC, area under the curve

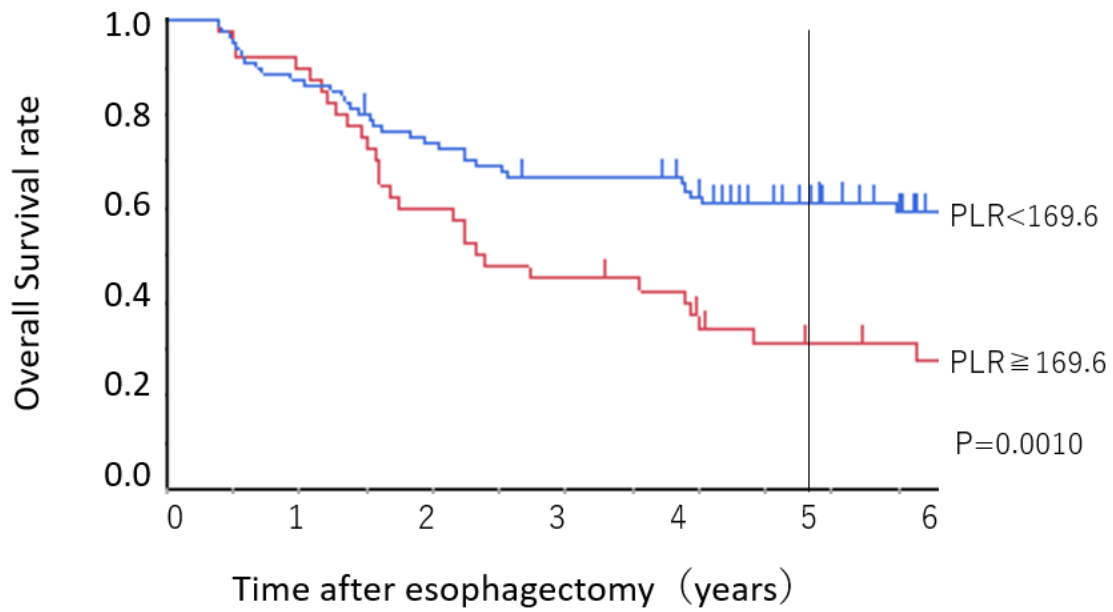


Figure 2b. Kaplan–Meier curve analysis was performed to evaluate overall survival differences among 121 patients who received NAC. Patients were divided into two groups according to the PLR cutoff value of 169.6. Those with a PLR ≥ 169.6 (31%) exhibited worse overall survival than those with a PLR < 169.6 (61%, $p=0.0010$). NAC, neoadjuvant chemotherapy; PLR, platelet-to-lymphocyte ratio

Table I. Characteristics of 174 patients who were grouped based on the PLR cutoff value

Characteristics	N=174	PLR ≥ 169.6 (n=58)	PLR < 169.6 (n=116)	<i>p</i>
	n (%)	n (%)	n (%)	
Sex				
Male/female	154 (89%) / 20 (11%)	50 (86%) / 8 (14%)	104 (90%) / 12 (10%)	0.5014
Age (years)				
≥ 63/< 63	121 (70%) / 53 (30%)	41 (71%) / 17 (29%)	80 (69%) / 36 (31%)	0.8158
Tumor location				0.8480
Upper	30 (17%)	11 (19%)	19 (16%)	
Middle	86 (50%)	27 (47%)	59 (51%)	
Lower	58 (33%)	20 (34%)	38 (33%)	
Tumor invasion depth*				0.1036
pT1	105 (60%)	33 (57%)	72 (62%)	
pT2	12 (7%)	4 (7%)	8 (7%)	
pT3	54 (31%)	18 (31%)	36 (31%)	
pT4	3 (2%)	3 (5%)	0 (0%)	
Lymph node metastasis*				0.0542
pN0	88 (51%)	29 (50%)	59 (51%)	
pN1	57 (33%)	16 (27%)	51 (35%)	
pN2	21 (12%)	12 (21%)	9 (8%)	
pN3	8 (4%)	1 (2%)	7 (6%)	
Leakage**				
+/-	29 (17%) / 145 (83%)	7 (12%) / 51 (88%)	22 (19%) / 94 (81%)	0.2499
Pneumonia**				
+/-	50 (29%) / 124 (71%)	17 (29%) / 41 (71%)	33 (28%) / 83 (72%)	0.9057
Operative time (min)				0.0664
≥ 740/< 740	56 (32%) / 118 (68%)	24 (41%) / 34 (59%)	32 (28%) / 84 (72%)	
Intraoperative blood loss				0.1532

(mL)			
≥ 415/< 415	68 (39%) / 106 (61%)	27 (47%) / 31 (53%)	41 (35%) / 75 (65%)

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. PLR, platelet-to-lymphocyte ratio

Table II. Univariate and multivariate analyses of prognostic factors for overall survival in 174 patients

Factors		Cases	Overall survival					
		N=174	Univariate analysis			Multivariate analysis		
			Hazard ratio (95% CI)		<i>p</i>	Hazard ratio (95% CI)		<i>p</i>
Sex								
Male/female		154/20	1.049	(0.503– 2.188)	0.897			
Age (years)								
≥ 63/< 63		121/53	1.403	(0.833– 2.365)	0.202			
Tumor location					0.528			
Upper		30	1.000					
Middle		86	1.152	(0.598– 2.220)	0.671			
Lower		58	1.432	(0.725– 2.828)	0.300			
PLR (ng/ml)								
≥ 169.6/< 169.6		58/116	1.829	(1.155– 2.895)	0.011	1.812	(1.063– 3.089)	0.028
Tumor invasion depth			<0.0001			<0.0001		
pT1		105	1.000			1.000		
pT2		12	2.197	(0.903– 5.347)	0.082	2.333	(0.923– 5.897)	0.073
pT3		54	5.290	(3.184– 8.790)	<0.0001	4.655	(2.625– 8.254)	<0.0001
pT4		3	10.784	(3.231– 35.993)	0.0001	8.130	(2.178– 30.346)	0.001
Lymph node metastasis			<0.0001			<0.0001		
pN0		88	1.000			1.000		
pN1		57	1.490	(0.850– 2.613)	0.163	1.239	(0.689– 2.229)	0.472
pN2		21	5.742	(3.102–	<0.0001	2.198	(1.084–	0.029

			10.629)		4.458)		
pN3	8	13.767	(5.833–	<0.0001	18.287	(6.879–	<0.0001
		32.492)			48.614)		
Leakage*							
+/-	28/145	0.593	(0.294–	0.143			
		1.194)					
Pneumonia*							
+/-	50/124	1.497	(0.928–	0.097	1.791	(1.086–	0.022
		2.416)			2.953)		
Operative time (min)							
≥ 740/< 740	56/118	1.935	(1.221–	0.004	1.819	(1.095–	0.020
		3.068)			3.021)		
Intraoperative blood loss (mL)							
≥ 415/< 415	68/106	1.895	(1.199–	0.006	1.587	(0.962–	0.070
		2.995)			2.616)		

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. CI, confidence interval

Table III. Characteristics of 121 patients who received neoadjuvant chemotherapy grouped by PLR

Characteristics	Cases N=121 n (%)	PLR ≥ 169.6 (n=40) n (%)	PLR < 169.6 (n=81) n (%)	<i>p</i>
Sex				0.8222
Male/female	107 (88%) / 14 (12%)	35 (88%) / 5 (12%)	72 (89%) / 9 (11%)	
Age (years)				
≥ 63/< 63	86 (71%) / 35 (29%)	31 (78%) / 9 (22%)	55 (68%) / 26 (32%)	0.2733
Tumor location				0.6262
Upper	17 (14%)	7 (17%)	10 (12%)	
Middle	58 (48%)	17 (43%)	41 (51%)	
Lower	46 (38%)	16 (40%)	30 (37%)	
Tumor invasion depth*				0.0969
pT1	57 (47%)	18 (45%)	36 (60%)	
pT2	11 (9%)	3 (7.5%)	4 (7%)	
pT3	50 (41%)	16 (40%)	20 (33%)	
pT4	3 (3%)	3 (7.5%)	0 (0%)	
Lymph node metastasis*				0.1884
N0	50 (41%)	16 (40%)	34 (41%)	
N1	45 (37%)	13 (33%)	32 (37%)	
N2	19 (16%)	10 (25%)	9 (16%)	
N3	7 (6%)	1 (2%)	6 (6%)	
Leakage**				0.1916
+/-	16 (13%) / 105 (87%)	3 (8%) / 37 (92%)	13 (16%) / 68 (84%)	
Pneumonia**				0.6422
+/-	36 (30%) / 85 (70%)	13 (32%) / 27 (68%)	23 (28%) / 58 (72%)	
Operative time (min)				0.0820
≥ 711/< 711	56 (46%) / 65	23 (58%) / 17	33 (41%) / 48	

	(54%)	(42%)	(59%)	
Intraoperative blood loss (mL)				0.0233
≥ 415 / < 415	52 (43%) / 69 (57%)	23 (58%) / 27 (42%)	29 (36%) / 52 (64%)	

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. PLR, platelet-to-lymphocyte ratio

Table IV. Univariate and multivariate analyses of prognostic factors for overall survival in 121 patients following neoadjuvant chemotherapy

Factors	Cases N=121	Overall survival			
		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>p</i>	Hazard ratio (95% CI)	<i>p</i>
Sex					
Male/female	107/14	1.012 (0.460– 2.226)	0.975		
Age (years)					
≥ 63/< 63	86/35	1.623 (0.894– 2.944)	0.111		
Tumor location			0.904		
Upper	17	1.000			
Middle	58	1.169 (0.554– 2.467)	0.680		
Lower	46	1.174 (0.542– 2.542)	0.682		
PLR (ng/mL)					
≥ 169.6/< 169.6	40/81	2.270 (1.376– 3.745)	0.0013	2.350 (1.293– 4.243)	0.005
Tumor invasion depth*			<0.0001		0.0161
pT1	57	1.000		1.000	
pT2	11	1.898 (0.752– 4.792)	0.174	2.075 (0.800– 5.381)	0.133
pT3	50	3.767 (2.106– 6.738)	<0.0001	2.794 (1.438– 5.429)	0.002
pT4	3	7.912 (2.305– 27.158)	0.001	3.848 (0.968– 15.291)	0.055
Lymph node metastasis*			<0.0001		<0.0001
N0	50	1.000		1.000	
N1	45	1.650 (0.865– 3.147)	0.128	1.640 (0.835– 3.223)	0.150
N2	19	5.829 (2.880– 11.797)	<0.0001	3.072 (1.378– 6.849)	0.006

N3	7	38.124 (13.220– 109.937)	<0.0001	42.115 (12.890– 137.596)	<0.0001
Leakage**					
+/-	16/105	0.627 (0.269– 1.460)	0.279		
Pneumonia**					
+/-	36/85	1.680 (0.997– 2.830)	0.051	1.615 (0.915– 2.853)	0.098
Operative time (min)					
≥ 711/< 711	56/65	1.859 (1.123– 3.078)	0.015	1.454 (0.811– 2.608)	0.208
Intraoperative blood loss (mL)					
≥ 415/< 415	52/69	1.946 (0.179– 3.213)	0.009	1.775 (1.008– 3.126)	0.046

*The stages were grouped by 8th edition of Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. CI, confidence interval

Table I. Characteristics of 174 patients who were grouped based on the PLR cutoff value

Characteristics	N=174	PLR $\geq$ 169.6 (n=58)	PLR < 169.6 (n=116)	<i>p</i> - <i>value</i>
	n (%)	n (%)	n (%)	
Sex				
Male/female	154 (89%) / 20 (11%)	50 (86%) / 8 (14%)	104 (90%) / 12 (10%)	0.5014
Age (years)				
≥ 63 / < 63	121 (70%) / 53 (30%)	41 (71%) / 17 (29%)	80 (69%) / 36 (31%)	0.8158
Tumor location				0.8480
Upper	30 (17%)	11 (19%)	19 (16%)	
Middle	86 (50%)	27 (47%)	59 (51%)	
Lower	58 (33%)	20 (34%)	38 (33%)	
Tumor invasion depth*				0.1036
pT1	105 (60%)	33 (57%)	72 (62%)	
pT2	12 (7%)	4 (7%)	8 (7%)	
pT3	54 (31%)	18 (31%)	36 (31%)	
pT4	3 (2%)	3 (5%)	0 (0%)	
Lymph node metastasis*				0.0542
pN0	88 (51%)	29 (50%)	59 (51%)	
pN1	57 (33%)	16 (27%)	51 (35%)	
pN2	21 (12%)	12 (21%)	9 (8%)	
pN3	8 (4%)	1 (2%)	7 (6%)	
Leakage**				
+/-	29 (17%) / 145	7 (12%) / 51	22 (19%) / 94	0.2499

	(83%)	(88%)	(81%)	
Pneumonia**				
+/-	50 (29%) / 124 (71%)	17 (29%) / 41 (71%)	33 (28%) / 83 (72%)	0.9057
Operative time (min)				0.0664
≥ 740/< 740	56 (32%) / 118 (68%)	24 (41%) / 34 (59%)	32 (28%) / 84 (72%)	
Intraoperative blood loss (ml)				0.1532
≥ 415/< 415	68 (39%) / 106 (61%)	27 (47%) / 31 (53%)	41 (35%) / 75 (65%)	

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. PLR, platelet-to-lymphocyte ratio

Table II. Univariate and multivariate analyses of prognostic factors for overall survival in 174 patients

Factors		Cases	Overall survival			
		N=174	Univariate analysis		Multivariate analysis	
			Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value
Sex						
Male/female		154/20	1.049 (0.503– 2.188)	0.897		
Age (years)						
≥ 63/< 63		121/53	1.403 (0.833– 2.365)	0.202		
Tumor location				0.528		
Upper		30	1.000			
Middle		86	1.152 (0.598– 2.220)	0.671		
Lower		58	1.432 (0.725– 2.828)	0.300		
PLR (ng/ml)						
≥ 169.6/< 169.6		58/116	1.829 (1.155– 2.895)	0.011	1.812 (1.063– 3.089)	0.028
Tumor invasion depth				<0.0001		<0.0001
pT1		105	1.000		1.000	
pT2		12	2.197 (0.903– 5.347)	0.082	2.333 (0.923– 5.897)	0.073

pT3	54	5.290 (3.184– 8.790)	<0.0001	4.655 (2.625– 8.254)	<0.0001
pT4	3	10.784 (3.231– 35.993)	0.0001	8.130 (2.178– 30.346)	0.001
Lymph node metastasis			<0.0001		<0.0001
pN0	88	1.000		1.000	
pN1	57	1.490 (0.850– 2.613)	0.163	1.239 (0.689– 2.229)	0.472
pN2	21	5.742 (3.102– 10.629)	<0.0001	2.198 (1.084– 4.458)	0.029
pN3	8	13.767 (5.833– 32.492)	<0.0001	18.287 (6.879– 48.614)	<0.0001
Leakage*					
+/-	28/145	0.593 (0.294– 1.194)	0.143		
Pneumonia*					
+/-	50/124	1.497 (0.928– 2.416)	0.097	1.791 (1.086– 2.953)	0.022
Operative time (min)					
≥ 740/< 740	56/118	1.935 (1.221– 3.068)	0.004	1.819 (1.095– 3.021)	0.020
Intraoperative					

blood loss (ml)							
≥ 415/< 415	68/106	1.895	(1.199–	0.006	1.587	(0.962–	0.070
		2.995)			2.616)		

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. CI, confidence interval

Table III. Characteristics of 121 patients who received neoadjuvant chemotherapy grouped by PLR

Characteristics	Cases N=121 n (%)	PLR ≥ 169.6 (n=40) n (%)	PLR < 169.6 (n=81) n (%)	<i>p-value</i>
Sex				0.8222
Male/female	107 (88%) / 14 (12%)	35 (88%) / 5 (12%)	72 (89%) / 9 (11%)	
Age (years)				
≥ 63/< 63	86 (71%) / 35 (29%)	31 (78%) / 9 (22%)	55 (68%) / 26 (32%)	0.2733
Tumor location				0.6262
Upper	17 (14%)	7 (17%)	10 (12%)	
Middle	58 (48%)	17 (43%)	41 (51%)	
Lower	46 (38%)	16 (40%)	30 (37%)	
Tumor invasion depth*				0.0969
pT1	57 (47%)	18 (45%)	36 (60%)	
pT2	11 (9%)	3 (7.5%)	4 (7%)	
pT3	50 (41%)	16 (40%)	20 (33%)	
pT4	3 (3%)	3 (7.5%)	0 (0%)	
Lymph node metastasis*				0.1884
N0	50 (41%)	16 (40%)	34 (41%)	
N1	45 (37%)	13 (33%)	32 (37%)	
N2	19 (16%)	10 (25%)	9 (16%)	

N3	7 (6%)	1 (2%)	6 (6%)	
Leakage**				0.1916
+/-	16 (13%) / 105 (87%)	3 (8%) / 37 (92%)	13 (16%) / 68 (84%)	
Pneumonia**				0.6422
+/-	36 (30%) / 85 (70%)	13 (32%) / 27 (68%)	23 (28%) / 58 (72%)	
Operative time (min)				0.0820
≥ 711/< 711	56 (46%) / 65 (54%)	23 (58%) / 17 (42%)	33 (41%) / 48 (59%)	
Intraoperative blood loss (ml)				0.0233
≥ 415/< 415	52 (43%) / 69 (57%)	23 (58%) / 27 (42%)	29 (36%) / 52 (64%)	

*Stages were grouped according to the 8th edition of the Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. PLR, platelet-to-lymphocyte ratio

Table IV. Univariate and multivariate analyses of prognostic factors for overall survival in 121 patients following neoadjuvant chemotherapy

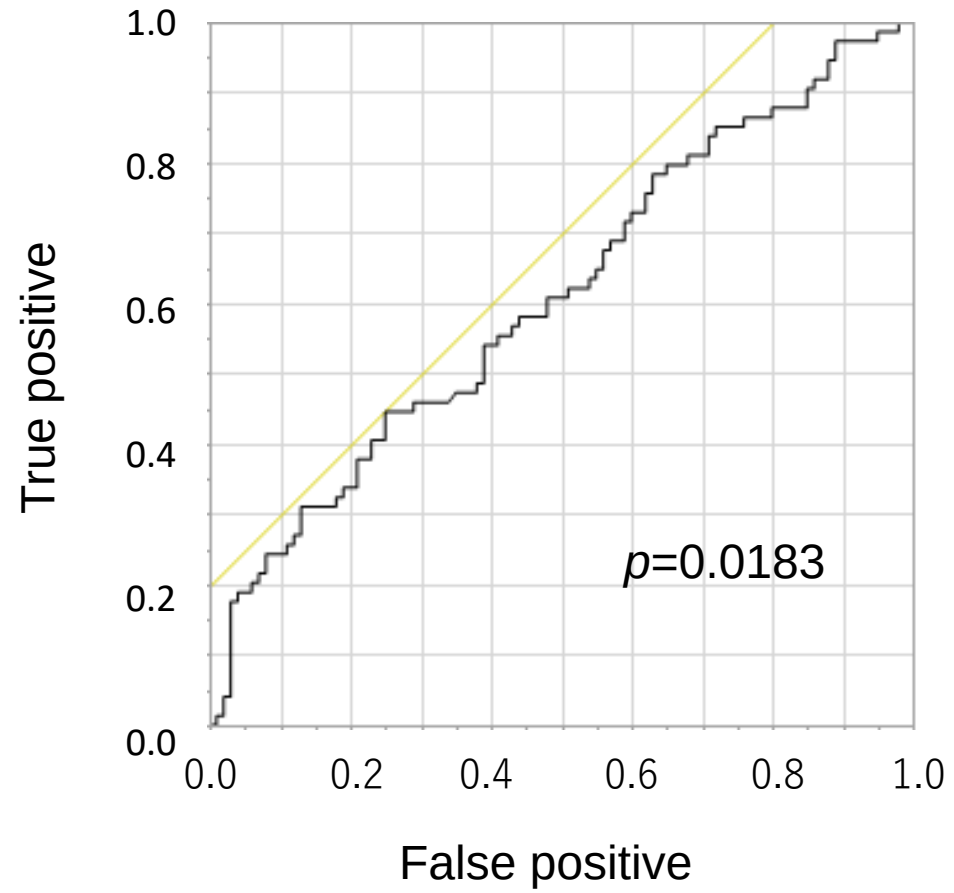
Factors	Cases	Overall survival			
		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>p-value</i>	Hazard ratio (95% CI)	<i>p-value</i>
Sex					
Male/female	107/14	1.012 (0.460– 2.226)	0.975		
Age (years)					
≥ 63/< 63	86/35	1.623 (0.894– 2.944)	0.111		
Tumor location					
Upper	17	1.000			
Middle	58	1.169 (0.554– 2.467)	0.680		
Lower	46	1.174 (0.542– 2.542)	0.682		
PLR (ng/ml)					
≥ 169.6/< 169.6	40/81	2.270 (1.376– 3.745)	0.0013	2.350 (1.293– 4.243)	0.005
Tumor invasion depth*					
pT1	57	1.000		1.000	
pT2	11	1.898 (0.752– 4.792)	0.174	2.075 (0.800– 5.381)	0.133
pT3	50	3.767 (2.106– 6.738)	<0.0001	2.794 (1.438– 5.429)	0.002
pT4	3	7.912 (2.305– 27.81)	0.001	3.848 (0.968– 15.11)	0.055

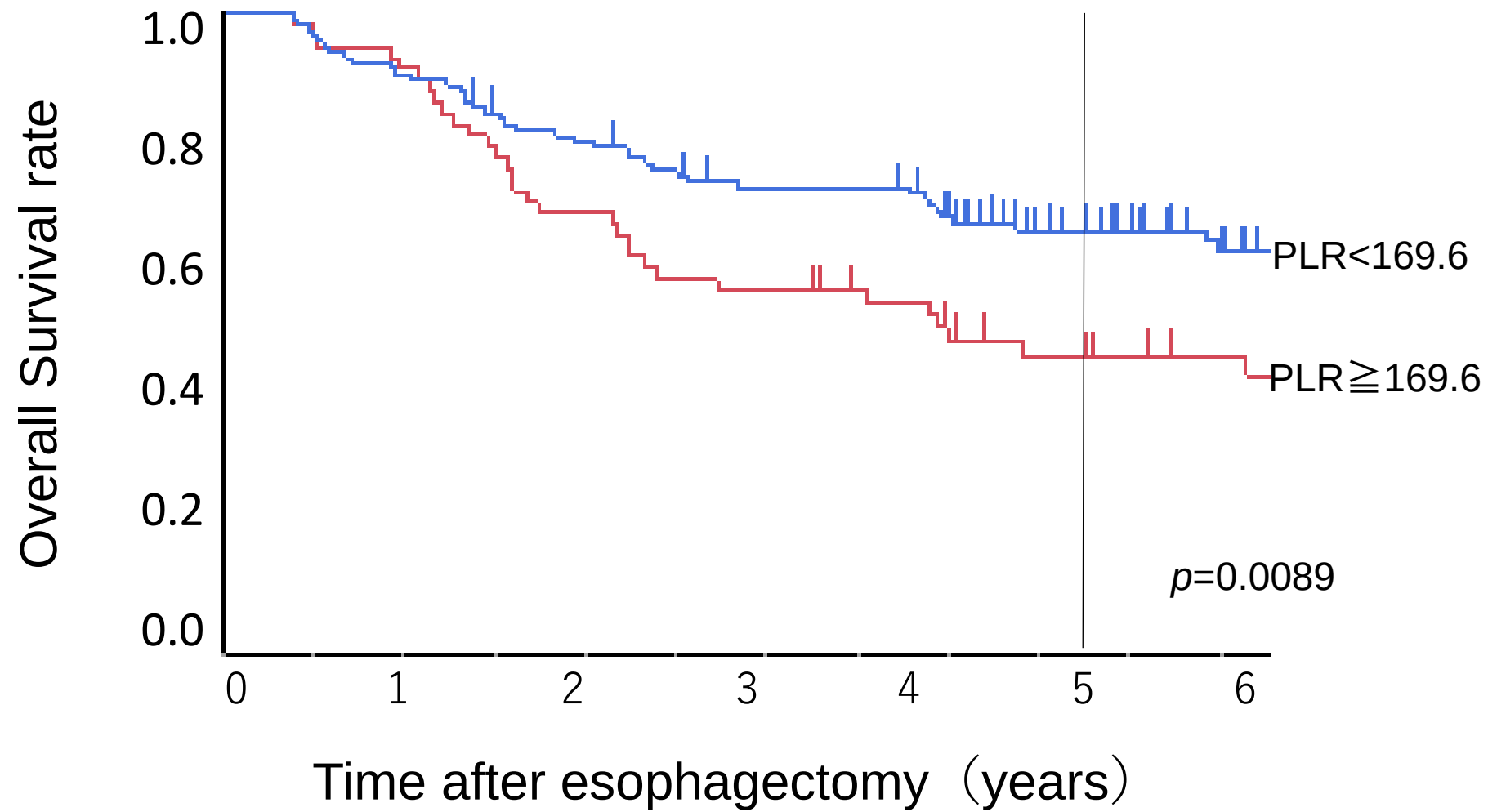
		27.158)	15.291)
Lymph node metastasis*		<0.0001	<0.0001
N0	50	1.000	1.000
N1	45	1.650 (0.865– 0.128 3.147)	1.640 (0.835– 0.150 3.223)
N2	19	5.829 (2.880– <0.0001 11.797)	3.072 (1.378– 0.006 6.849)
N3	7	38.124 (<0.0001 (13.220– 109.937)	42.115 (<0.0001 (12.890– 137.596)
Leakage**			
+/-	16/105	0.627 (0.269– 0.279 1.460)	
Pneumonia**			
+/-	36/85	1.680 (0.997– 0.051 2.830)	1.615 (0.915– 0.098 2.853)
Operative time (min)			
≥ 711/< 711	56/65	1.859 (1.123– 0.015 3.078)	1.454 (0.811– 0.208 2.608)
Intraoperative blood loss (ml)			
≥ 415/< 415	52/69	1.946 (0.179– 0.009 3.213)	1.775 (1.008– 0.046 3.126)

*The stages were grouped by 8th edition of Union for International Cancer Control TNM classification of malignant tumors.

**The postoperative complications were recognized when the Clavien–Dindo classification was higher than grade II. CI, confidence interval

ROC Curve





ROC Curve

