Impact of Antiplatelet and Anticoagulant Therapies on Platelet-related Prognostic Markers in Patients With Esophageal Cancer

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Abstract. *Background/Aim:* In recent years, platelet-related markers were recognized as useful prognostic factors in various malignancies. We investigated the relationship between platelet-related prognostic markers and anti-platelet or anti-coagulant therapies for survival outcomes in esophageal squamous cell carcinoma. *Patients and Methods:* Preoperative platelet-related prognostic markers were evaluated from peripheral blood testing and statistical analyses were performed to evaluate the prognostic value of these markers and reveal the effects of antiplatelets and/or anticoagulants regarding their prognostic relevance. *Results:* In all 176 patients, preoperative platelet-to-lymphocyte ratio (PLR) was not found to be a predictor of overall survival (OS). However, in patients without antiplatelet or anticoagulant therapies, PLR was significantly associated with a poor OS ($p=0.03$). Although platelet large cell ratio (P-LCR) was not associated with the prognosis in patients with antiplatelet and/or anticoagulant therapies, higher P-LCR was associated with a poor prognosis in patients without antiplatelet or anticoagulant therapies ($p<0.0001$). *Conclusion:* Researching detailed antiplatelet and anticoagulant therapies could reinforce the prognostic value of platelet-related prognostic markers in ESCC.

Esophageal cancer is the eighth most common diagnosed cancer in the world, with a persistent high mortality rate due to its late-stage diagnosis and rapid progression; the 5-year

survival rate ranges from 15% to 25%. Recently, several immunoinflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein-to-albumin ratio (CAR), have been reported to have prognostic relevance in various malignancies (1-8). However, several studies have failed to discover the prognostic value of PLR in esophageal cancer (9-11). Although immunoinflammatory markers are easily affected by various factors, such as neoadjuvant chemotherapy (NAC), smoking history, comorbidities, and the use of antiplatelet and anticoagulant drugs, little is known regarding the effect of these factors on the prognostic relevance of immunoinflammatory markers. In recent years, antiplatelet and anticoagulant therapies have been reported to reduce cardiovascular events, and the number of patients taking these drugs has increased (12, 13).

The present study aimed to investigate the effect of antiplatelet and anticoagulant drug use on platelet-related prognostic markers such as PLR, platelet distribution width (PDW), mean platelet volume (MPV), and platelet large cell ratio (P-LCR) in patients with resectable esophageal squamous cell carcinoma (ESCC).

Patients and Methods

Patients. A total of 176 patients diagnosed with ESCC who underwent curative transthoracic esophageal resection at the National Defense Medical College Hospital (Tokorozawa, Japan) from January 2009 to December 2016 were included in the present study. The mean±standard deviation age was 70.1±8.4 years (range=43-90 years). Of the 176 patients, 25 (14%) were women and 151 (86%) were men. NAC using 5-fluorouracil and cisplatin was administered to 95 (54%) patients; the remaining 81 (46%) did not receive NAC (14). The tumor node metastasis criteria from the eighth edition of the Union for International Cancer Control classification system were used for tumor staging (15). One hundred twenty-seven (72%) patients underwent video-assisted thoracoscopic esophagectomy, and 49 (28%) underwent conventional open transthoracic surgery. We preoperatively evaluated platelet-related prognostic markers,

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including PLR, PDW, MPV, and P-LCR. In the patients who underwent NAC, we used the sample before the first infusion of chemotherapy to avoid the effect associated with NAC. The history of antiplatelet and anticoagulant use was described according to the medical and nursing charts, and the patients were interviewed by the doctors in charge.

All the patient demographics were collected from a computer database, including pathological findings, surgical procedures, and overall survival (OS). The OS time was calculated from the day of surgery to the day of death due to any cause. Cancer-specific survival (CSS) time was calculated from the day of surgery to the day of death due to any cancerous cause. Patients who survived were all censored in our survival analyses. All the patients in this study were observed at our hospital or at the outpatient clinic at 3- or 4-month intervals during the first 2 years of the study and every 6 or 12 months thereafter for 3 years. Tumor markers and computed tomography scans were performed every 6 months until 5 years after the surgical resection. After 5 years, annual follow-ups were performed through telephone conversations with the patients, the patient's family members, or their practitioners. Written informed consent was obtained from all patients. The Institutional Review Board of the National Defense Medical College Hospital approved this protocol.

Surgical procedure. We performed conventional open transthoracic esophagectomy with two- or three-field lymphadenectomy through the right fifth or sixth thoracotomy for 49 patients. When using video-assisted thoracoscopic surgery (VATS), three ports with diameters of 12 mm were inserted after each patient was in the prone position (16). After thoracoscopy, laparoscopy-assisted surgery for gastric tube reconstruction was performed (17). When using conventional open surgery, a circular stapler (CEEAA; Covidien, Tokyo, Japan) was used for either cervical or intrathoracic anastomosis, depending on the tumor location. For the VATS, the same stapler was used in the case of intrathoracic anastomosis; a hand-sewn anastomosis was employed in the case of cervical anastomosis.

Platelet-related prognostic markers. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. The optimal cutoff value for platelet-related prognostic markers was determined according to the time-dependent receiver operating characteristic (ROC) curve for censored 3-year survival (PLR, 151; platelets, 221,000 cells/ μ L; lymphocytes, 1,652 cells/ μ L; PDW, 11.0 fL; MPV, 9.8 fL; P-LCR, 27.8%).

Antiplatelet and anticoagulant therapies. Of the 176 patients included in this study, 28 (15.9%) underwent antiplatelet and/or anticoagulant therapies; 15 (8.5%) had antiplatelet therapy; 17 (9.6%) had anticoagulant therapy; 4 (2.3%) had both antiplatelet and anticoagulant therapy; and 148 (84.0%) had neither antiplatelet nor anticoagulant therapy. Within at least 1 week before surgery, these therapies were stopped to avoid the complications associated with major bleeding.

Statistical analysis. All statistical analyses were performed using JMP 14.0 (SAS Institute Inc., Cary, NC, USA). Time-dependent ROC curves for censored 3-year survival were constructed to estimate the optimal cutoff value of the preoperative PLR, platelet counts, lymphocyte counts, PDW, MPV, and P-LCR. The Mann-Whitney *U* or Chi-squared tests were used for the statistical analyses. Hazard ratios (HR) with 95% confidence intervals (95% CI) and OS curves using the Kaplan-Meier method were employed.

Differences were compared using the log-rank test. Not only Log-rank test, Wilcoxon tests were also performed to balance for the low number of included patients as well as patients with comorbidities, and further validate presented data with statistical significance. Univariate and multivariate analyses were performed to determine the most influential factor on the prognosis. All *p* values of <0.05 were considered statistically significant.

Results

The relationships between clinicopathological characteristics and patient groups based on PLR, platelet counts, PDW, MPV, and P-LCR are shown in Table I. Preoperative PLR, platelet counts, PDW, and MPV had strong associations with pathological tumor depth ($p=0.02$, $p=0.03$, $p=0.0002$, $p=0.02$, respectively). PLR and P-LCR were associated with the pathological stage ($p=0.01$, $p=0.02$, respectively). PLR, PDW, and MPV were associated with the frequency of NAC ($p=0.01$, $p=0.002$, $p=0.02$, respectively).

The platelet counts and mean values of PDW, MPV, and P-LCR did not differ between the patients receiving antiplatelet and/or anticoagulant therapies and those who did not (Table II). The predictive values for OS of the PLR, platelet counts, PDW, MPV, and P-LCR were assessed by the area under the ROC (AUROC) curve (Figure 1). The AUROC of P-LCR was highest (AUROC=0.632) compared with that of PLR, platelets, PDW, and MPV (AUROC=0.539, 0.529, 0.559, 0.534, respectively).

Although preoperative PLR was not associated with the OS in patients with antiplatelet and/or anticoagulant therapies ($p=0.42$, respectively), PLR was significantly associated with OS in patients without these therapies ($p=0.03$) (Figure 2). In addition, PLR was associated with CSS in patients without either therapy, but not in patients with antiplatelet and/or anticoagulant therapies (Figure 3).

Platelet counts, PDW, and MPV did not affect the prognosis even when considering the use of antiplatelet and anticoagulant therapies (Figure 4). Although patients without antiplatelet or anticoagulant therapies ($p<0.0001$) with high P-LCR had a poorer survival than those with low P-LCR, P-LCR was not associated with the prognosis in patients with antiplatelet and/or anticoagulant therapies ($p=0.69$).

To remove the effect of antiplatelet and/or anticoagulant therapies on the result, we performed univariate and multivariate analyses of factors in patients without antiplatelet or anticoagulant therapies; tumor depth and P-LCR were independent prognostic factors and PLR was not (Table III).

Discussion

In the present study, we investigated the impact of antiplatelet and anticoagulant therapies on the prognostic value of platelet-related markers in patients who underwent

Table 1. Clinicopathological characteristics according to the PLR, platelet counts, PDW, MPV, and P-LCR.

	Cases (number, %)		PLR		p-Value	Platelet		p-Value	PDW		p-Value	MPV		p-Value	PLCR		p-Value
	<151	≥151	<151	≥151		<211,000	≥211,000		<11.0	≥11.0		<9.8	≥9.8		<27.8	≥27.8	
Gender																	
Female	25 (14)	9 (13)	16 (15)	0.66		8 (12)	17 (15)	0.51	16 (15)	9 (12)	0.66	15 (16)	10 (12)	0.67	18 (15)	7 (13)	0.82
Male	151 (86)	62 (87)	89 (85)			61 (88)	90 (85)		87 (85)	64 (88)		80 (84)	71 (88)		103 (85)	48 (87)	
Age (years)																	
<65	40 (23)	12 (17)	28 (27)	0.14		14 (20)	26 (24)	0.58	25 (24)	15 (21)	0.59	25 (26)	15 (19)	0.28	32 (26)	8 (15)	0.11
≥65	136 (77)	59 (83)	77 (73)			55 (80)	81 (76)		78 (76)	58 (79)		70 (74)	66 (81)		89 (74)	47 (85)	
T stage																	
T1	59 (34)	31 (44)	28 (27)	0.02		29 (42)	30 (28)	0.03	23 (22)	36 (49)	0.00	24 (25)	35 (43)	0.02	43 (36)	16 (29)	0.10
T2	22 (13)	11 (15)	11 (10)			11 (16)	11 (10)		15 (15)	7 (10)		16 (17)	6 (7)		15 (12)	7 (13)	
T3	82 (47)	27 (38)	55 (52)			27 (39)	55 (51)		55 (53)	27 (37)		50 (53)	32 (40)		58 (48)	24 (44)	
T4	13 (6)	2 (3)	11 (11)			2 (3)	11 (11)		10 (10)	3 (4)		5 (5)	8 (10)		5 (4)	8 (15)	
Lymph node metastasis																	
N0	72 (41)	37 (52)	35 (33)	0.09		33 (48)	39 (36)	0.52	39 (38)	33 (45)	0.57	37 (39)	35 (43)	0.55	52 (43)	20 (36)	0.12
N1	47 (27)	14 (20)	33 (31)			16 (23)	31 (29)		30 (29)	17 (23)		25 (26)	22 (27)		35 (29)	12 (22)	
N2	34 (19)	12 (17)	22 (21)			12 (17)	22 (21)		22 (21)	12 (16)		22 (23)	12 (15)		23 (19)	11 (20)	
N3	23 (13)	8 (11)	15 (14)			8 (12)	15 (14)		12 (12)	11 (16)		11 (12)	12 (15)		11 (9)	12 (22)	
TNM stage																	
I	45 (26)	24 (34)	21 (20)	0.01		23 (33)	22 (21)	0.20	19 (18)	26 (36)	0.06	20 (21)	25 (31)	0.20	34 (28)	11 (20)	0.02
II	39 (22)	20 (28)	19 (18)			16 (23)	23 (22)		23 (22)	16 (22)		22 (23)	17 (21)		26 (21)	13 (24)	
III	73 (41)	23 (32)	50 (48)			25 (36)	48 (45)		49 (48)	24 (33)		45 (47)	28 (35)		54 (45)	19 (35)	
IV	19 (11)	4 (6)	15 (14)			5 (8)	14 (12)		12 (12)	7 (10)		8 (8)	11 (14)		7 (6)	12 (22)	
Tumor location																	
Upper	28 (16)	13 (18)	15 (14)	0.47		13 (19)	15 (14)	0.55	12 (12)	16 (22)	0.18	13 (14)	15 (19)	0.41	18 (15)	10 (18)	0.39
Middle	74 (42)	32 (45)	42 (40)			26 (38)	48 (45)		46 (45)	28 (38)		44 (46)	30 (37)		48 (40)	26 (47)	
Lower	74 (42)	26 (37)	48 (46)			30 (43)	44 (41)		45 (44)	29 (40)		38 (40)	36 (44)		55 (45)	19 (35)	
Tumor differentiation																	
Well	15 (9)	6 (8)	9 (9)	0.32		7 (10)	8 (8)	0.33	9 (9)	6 (8)	0.99	6 (6)	9 (11)	0.09	12 (10)	3 (5)	0.44
Moderate	144 (82)	61 (86)	83 (79)			58 (84)	86 (80)		84 (82)	60 (82)		76 (80)	68 (84)		96 (79)	48 (88)	
Poor	17 (9)	4 (6)	13 (12)			4 (6)	13 (12)		10 (10)	7 (10)		13 (14)	4 (5)		13 (11)	4 (7)	
Surgical procedure																	
Open	49 (28)	18 (25)	31 (30)	0.61		24 (35)	25 (23)	0.12	30 (29)	19 (26)	0.73	34 (30)	15 (25)	0.60	33 (27)	16 (29)	0.86
Video-assisted	127 (72)	53 (75)	74 (70)			45 (65)	87 (77)		73 (71)	54 (74)		81 (70)	46 (75)		88 (73)	39 (71)	
Neoadjuvant chemotherapy																	
Yes	95 (54)	30 (42)	65 (62)	0.01		31 (45)	64 (60)	0.06	66 (64)	29 (40)	0.00	59 (62)	45 (56)	0.02	70 (58)	25 (45)	0.14
No	81 (46)	41 (58)	40 (38)			38 (55)	43 (40)		37 (36)	44 (60)		36 (38)	36 (44)		51 (42)	30 (55)	

TNM, Tumor, node, and metastasis; PLR, platelet-to-lymphocyte ratio; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio.

Figure 1. Time-dependent ROC for censored 3 years survival and AUROC were evaluated to verify the accuracy of PLR, platelet counts, PDW, MPV, and P-LCR for survival prediction. AUROC of P-LCR was highest compared with that of PLR, platelets, PDW, and MPV. ROC, Receiver operating curve; AUROC, area under the ROC; PLR, platelet-to-lymphocyte ratio; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio.

Table II. Comparison of platelet counts, PDW, MPV, and P-LCR between patients with antiplatelet and/or anticoagulant therapies and patients without antiplatelet or anticoagulant therapies.

	Patient number	Platelet count	<i>p</i> -Value	PDW	<i>p</i> -Value	MPV	<i>p</i> -Value	PLCR	<i>p</i> -Value
With antiplatelet and/or anticoagulant therapies	28	243,000±16,226	0.70	11.06±0.35	0.67	10.0±0.17	0.63	26.5±1.52	0.1
Without antiplatelet nor anticoagulant therapies	148	249,612±7,058		10.89±0.15		9.9±0.07		23.9±0.66	

PDW, Platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio.

curative esophageal resection for ESCC. We found that although PLR was not associated with OS in the overall cohort, PLR was significantly associated with OS in patients who had not been administered antiplatelet and/or anticoagulant medications.

Increasing numbers of studies have reported the prognostic value of PLR in various malignancies; however, the biological mechanism of this phenomenon remains controversial (9, 18-

21). Feng *et al.* (2) investigated the prognostic value of NLR and PLR in patients with esophageal cancer and concluded that they were significant predictors of OS in patients with esophageal cancer and that PLR was superior to NLR as a predictive factor, on the basis of ROC curves. On the other hand, several other studies did not report a prognostic value for PLR (9-11). Our previous systematic meta-analysis also showed that an absence of association between PLR and OS,

Figure 2. Overall survival after esophagectomy for ESCC according to preoperative PLR in all patients, patients with antiplatelet and/or anticoagulant therapies, and patients without antiplatelet or anticoagulant therapies. PLR was significantly associated with OS in patients without antiplatelet and/or anticoagulant therapies, but not in patients with antiplatelet and/or anticoagulant therapies. ESCC, Esophageal squamous cell carcinoma; PLR, platelet-to-lymphocyte ratio.

Figure 3. Cancer-specific survival after esophagectomy for ESCC according to preoperative PLR in all patients, patients with antiplatelet and/or anticoagulant therapies, and patients without antiplatelet nor anticoagulant therapies. PLR was associated with CSS in patients without either therapy, but not in patients with antiplatelet and/or anticoagulant therapies. ESCC, Esophageal squamous cell carcinoma; PLR, platelet-to-lymphocyte ratio.

though NLR and CAR was significantly associated with prognosis (22). In the present study, PLR was associated with the prognosis in patients without antiplatelet or anticoagulant therapies; in patients with these therapies; however, PLR was not related to prognosis.

We speculated that the platelet functional changes associated with antiplatelet or anticoagulant therapies may affect the clinical relevance of PLR in patients with these therapies. Neutrophil extracellular traps (NETs) are recently recognized mechanisms that are released from tumor-associated neutrophils and form a physical barrier between cancer cells and immunocompetent cells. Thus, cancer cells can escape the immune response due to the NET barrier and tumor migration is promoted (23). In a mouse model, Lapponi *et al.* (24) and Caudrillier *et al.* (25) reported inhibition of NET formation by antiplatelet drugs. Similar theories have also been reported regarding platelet cells.

Holmes *et al.* (26) reported that platelet cells provide a procoagulant surface, increasing amplification of cancer-related coagulation, and they can be recruited to tumor cells, shielding them from immune responses and improving cancer growth and dissemination. Wenzel *et al.* reported success in reducing pulmonary metastases in a murine model of breast cancer using the antiplatelet drug, cilostazol, which decreased platelet aggregability and platelet-tumor complex formation (27). In clinical research, many reports have demonstrated the benefit of antiplatelet drugs regarding incidence or mortality of malignancies, such as colorectal cancer, ovarian cancer, and esophageal cancer (28-30).

PDW, MPV, and P-LCR are often used to measure platelet size and as surrogate markers of platelet activation (31). Several studies have reported that high PDW and MPV were poor prognostic markers in various malignancies (32-34). P-LCR is often reported as a prognostic factor in coronary

Figure 4. Overall survival after esophagectomy for ESCC according to preoperative platelet counts, PDW, MPV, and P-LCR according to antiplatelet and anticoagulant use. Although patients without antiplatelet or anticoagulant therapies with high P-LCR had poorer survival than those with low P-LCR, P-LCR was not associated with the prognosis in patients with antiplatelet and/or anticoagulant therapies. ESCC, Esophageal squamous cell carcinoma; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio.

artery disease and myocardial infarction, but has never been associated with cancer prognoses (35).

To reveal how antiplatelet and/or anticoagulant therapies affect PLR, we further investigated PDW, MPV, and P-LCR, which we considered to be morphologically associated with PLR. From our results, platelet counts, PDW, and MPV were not related to prognosis even when considering antiplatelet

and/or anticoagulant therapies. High P-LCR levels in patients without antiplatelet or anticoagulant therapies were related to poor survival, but P-LCR was not associated with the prognosis in patients with these therapies; this result was very similar to that of PLR. Strangely, the mean values of P-LCR were not different according to the use of antiplatelet and/or anticoagulant therapies. The median survival time of

Table III. Univariate and multivariate analyses that could affect overall survival of patients with ESCC (patients without antiplatelet or anticoagulant therapies).

	Univariate analysis HR (95% CI)	p-Value	Multivariate analysis HR (95% CI)	p-Value
Gender				
Female	Ref.	0.0442	Ref.	0.0221
Male	2.361 (1.111-6.106)		2.400 (1.120-6.241)	
Age (years)				
<65	Ref.	0.3207		
≥65	1.343 (0.773-2.505)			
Tumor depth				
T1-T2	Ref.	<0.0001	Ref.	<0.0001
T3-T4	3.204 (1.916-5.620)		2.955 (1.736-5.262)	
Lymph node metastasis				
N0-N1	Ref.	0.0617		
N2-N3	1.586 (0.965-2.554)			
Tumor location				
Lower/ middle	Ref.	0.2019		
Upper	1.448 (0.790-2.490)			
Tumor differentiation				
Well/ moderate	Ref.	0.1053		
Poor	1.740 (0.837-3.246)			
Surgical procedure				
Video- assisted	Ref.	0.0743		
Open	1.536 (0.949-2.449)			
PLR				
<151	Ref.	0.0279	Ref.	0.0848
≥151	1.721 (1.059-2.880)		1.555 (0.942-2.642)	
PDW				
<11	Ref.	0.1430		
≥11	0.7021 (0.428-1.124)			
MPV				
<9.8	Ref.	0.5448		
≥9.8	0.8669 (0.541-1.374)			
PLCR				
<27.8	Ref.	<0.0001	Ref.	<0.0001
≥27.8	3.157 (1.957-5.065)		3.518 (2.138-5.773)	

ESCC, Esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; Ref., reference; PLR, platelet-to-lymphocyte ratio; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio.

patients with high P-LCR receiving antiplatelet therapies was 56.5 months, which was higher than that in patients without antiplatelet therapies (8.2 months). We speculated that large platelet cells might be associated with greater platelet-tumor complex formation than might normal-sized platelet cells; therefore, patients with high P-LCR could gain more benefit

from antiplatelet drugs than could patients with low P-LCR levels. Furthermore, in our study, we found that the AUROC of P-LCR was highest compared with other platelet-related factors and was the only independent prognostic factor among these measures in the multivariate analysis. Although P-LCR has never been associated with cancer prognoses, future studies should reveal the association between P-LCR and cancer prognoses, while also considering antiplatelet and/or anticoagulant therapies.

The present study had certain limitations. First, it was conducted at a single institution using a retrospective design, with a relatively small number of patients, especially patients undergoing antiplatelet and/or anticoagulant therapies. The patients who underwent antiplatelet or anticoagulant therapy sometimes had severe comorbidities, such as heart disease and cerebrovascular disease; therefore, indication for surgical resection was limited with them.

Second, the best approach to determine the cutoff value of PLR remains controversial. Most studies have used a time-dependent ROC curve, which is also the approach we adopted; however, several studies had used median values or cutoff value previously reported. Therefore, the PLR cutoff value varied from 120 to 244 in these studies, and these heterogeneities should be resolved in the future.

Third, Guo *et al.* reported that NLR and use of anti-biotic drugs effected on prognosis in ESCC patients. (1) Not only antiplatelet and/or anticoagulant therapies but also any other medications should be considered its effects on these values.

In conclusion, the investigation of preoperative platelet-related prognostic markers for survival outcomes might need to include the effects of antiplatelet and anticoagulant therapies. More and larger studies with a prospective analysis should be mandated to clearly confirm the results. In this study, in particular, the result that antiplatelet therapy might improve the prognoses of patients with high PLR and P-LCR who were primary worse than lower groups should be verified by future prospective clinical studies.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this article.

Authors' Contributions

YI, HT, HN, YY, KK, ST, YI, SF, SN, NI, MH, HS, and ES helped to draft the manuscript. YK and HU have revised manuscript critically. All Authors read and approved the final manuscript.

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