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Clinical Impact of Platelet-to-albumin Ratio on Esophageal Cancer Patients Who Receive Curative Treatment

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Abstract. *Background/Aim: Perioperative nutrition and inflammation affect the oncological outcomes of various malignancies. We evaluated the clinical impact of the preoperative platelet-to-albumin ratio (PAR) in resectable esophageal cancer patients who received curative treatment. Patients and Methods: This study included 168 patients who underwent curative surgery followed by perioperative adjuvant chemotherapy for esophageal cancer between 2005 and 2018. The risk factors for overall survival (OS) and recurrence-free survival (RFS) were identified. Results: Based on the 3- and 5-year OS rates, we set the cut-off value for the PAR at 80×10^3 in the present study. Among 168 patients, 134 (79.8%) were defined as the PAR-low and 34 (20.2%) as the PAR-high group. The 3- and 5-year OS rates were 60.2% and 51.7% in the PAR-low group and 30.2% and 18.9% in the PAR-high group, respectively. There were significant differences in OS (p=0.005). The PAR was therefore selected for the final multivariate analysis model [hazard ratio=1.997, 95% confidence interval (CI)=1.230-3.241, p=0.037]. On comparing the perioperative clinical course between the PAR-high and PAR-low groups, there were marginally significant differences in the postoperative surgical complications and intraoperative blood loss between the groups. Conclusion: The PAR had clinical influence on the long-term oncological outcomes of esophageal cancer patients and might thus be a promising prognostic factor for esophageal cancer patients.*

Esophageal cancer is the eighth-most common cancer and the sixth leading cause of cancer-related mortality worldwide (1, 2). Standard treatment for resectable esophageal cancer is perioperative adjuvant treatment and esophagectomy (3, 4). The survival rate after curative treatment has gradually improved thanks to improvements in perioperative management and perioperative adjuvant treatment and the introduction of minimally invasive surgery.

However, more than half of patients experience recurrence, even after curative treatment. Once a patient's disease recurs, the prognosis is poor (5, 6). Therefore, it is necessary to identify prognostic factors in order to introduce more aggressive treatment. Recently, perioperative nutrition and inflammation have been shown to be associated with oncological outcomes in various malignancies (7, 8). Previous studies demonstrated that perioperative malnutrition and systemic inflammation accelerated tumor growth and enhanced micrometastasis (9, 10). Therefore, assessing a patient's preoperative nutritional and inflammation status is important. If physicians can manage and control the perioperative nutrition and inflammation status using optimal screening tools, they may be able to improve a patient's survival. However, screening tools for evaluating both the perioperative nutrition status and inflammation status in esophageal cancer patients are limited at present.

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Key Words: Platelet-to-albumin ratio, esophageal cancer, prognostic factor.

Recently, the platelet-to-albumin ratio (PAR) was developed and reported as a promising prognostic factor in gastrointestinal malignancies (11-13). Previous reports have shown that platelets are a marker of the systemic inflammation status, and albumin is one of the most important markers of nutritional status. Both a hyperinflammatory status and hypoalbuminemia were confirmed to increase a patient's surgical risk and decrease the long-term survival. Therefore, the PAR might be able to assess both the nutritional status and systemic inflammation status. In addition, the PAR only involves the platelet count and albumin level, granting it several clinical advantages over other parameters, such as ease of implementation, preoperative accessibility, and low cost to evaluate.

We hypothesized that the preoperative PAR might have clinical impact on the oncological outcomes of esophageal cancer patients who received curative treatment. To confirm our hypothesis, we evaluated the prognostic value and clinical impact of the PAR in esophageal cancer patients who receive curative treatment.

Patients and Methods

Patients. Patients were selected from the medical records of consecutive patients diagnosed with primary esophageal adenocarcinoma or squamous cell carcinoma and who underwent complete resection at Yokohama City University from 2005 to 2018. Inclusion criteria were as follows: 1) stage I to III disease as evaluated according to the 7th edition of UICC classification, 2) complete (R0) resection of the esophageal cancer with lymphadenectomy, and 3) a laboratory blood analysis performed within one week before surgery. Patients who received R1 or R2 resection were excluded from the present analysis.

Surgical procedure. In principle, subtotal esophagectomy *via* right thoracotomy and reconstruction with a gastric tube is the standard procedure. Two-field lymph node dissection is indicated when tumors are located at the middle- to lower-thoracic esophagus, whereas three-field dissection is applied for upper-thoracic tumors.

Measurement of the PAR. The PAR was calculated by dividing the platelet count (10^3/ml) by the serum albumin level (g/l). PAR values were assessed within seven days before surgery.

Evaluations and statistical analyses. The significance of differences between the PAR and clinicopathological parameters was determined using the χ^2 test. The Kaplan-Meier method was used to calculate the overall survival (OS) and recurrence-free survival (RFS) curves. The OS was defined as the period between the date of surgery and death, and the RFS was defined as the period between surgery and the occurrence of an event, recurrence, or death, whichever came first. The data of patients who had not experienced an event were censored at the date of the final observation. The univariate and multivariate survival analyses were performed using a Cox proportional hazards model. *p*-Values of <0.05 were considered to indicate statistical significance.

The SPSS software program (v26.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses. This study was approved by the IRB of Yokohama City University.

Results

Patients. One-hundred and sixty-eight patients were evaluated in the present study. Based on the 3- and 5-year OS rate and previous reports, we set the cut-off value for the PAR at 80×10^3 (Table I). In the present study, the patients were divided into the PAR-low group ($<80\times10^3$) and PAR-high group ($\geq80\times10^3$). Among 168 patients, 134 (79.8%) were defined as the PAR-low and 34 (20.2%) as the PAR-high group. The patients' background characteristics were similar between the PAR-low and PAR-high groups. The median age (67 years old *vs*. 66 years old, p=0.424), male ratio (85.1% *vs*. 85.3%, p=0.974), alcohol habit incidence (89.6% *vs*. 79.4%, p=0.110), smoking habit incidence (86.6% *vs*. 85.3%, p=0.847), incidence of hypertension (47.8% *vs*. 47.1%, p=0.942), incidence of diabetes merits (14.9% *vs*. 14.7%, p=0.974), and incidence of chronic obstructive pulmonary disease (31.3% *vs*. 32.4%, p=0.910) were similar, whereas the preoperative median hemoglobin level (12.7g/dl *vs*. 11.5 g/dl, $p<0.001$), preoperative median white blood cell count (6070 *vs*. 7447, p=0.001) and preoperative median C-reactive protein (0.45 mg/dl *vs*. 1.4 mg/dl, $p<0.001$) were worse in the PAR-high group compared to those in the PAR-low group.

Results of a survival analysis between the PAR-low and PAR-high groups. The 3- and 5-year OS rates were 60.2% and 51.7% in the PAR-low group and 30.2% and 18.9% in the PAR-high group, respectively, showing significant differences in OS (Figure 1) (p=0.001). Each clinicopathological factor was categorized as shown in Table II and analyzed for its prognostic significance. The univariate analyses for OS showed that the pathological T status and PAR were significant prognostic factors. The PAR was therefore selected for the final multivariate analysis model [hazard ratio (HR)=1.997, 95% confidence interval (CI)=1.230-3.241, p=0.005].

The 3- and 5-year RFS rates were 44.8% and 37.4% in the PAR-low group and 18.4% and 13.8% in the PAR-high group, respectively, showing significant differences in RFS (Figure 2) (p=0.001). Each clinicopathological factor was categorized as shown in Table III and analyzed for its prognostic significance. The univariate analyses for RFS showed that the pathological T status, lymph node metastasis, and PAR were significant prognostic factors. The PAR was thus also selected for the final multivariate analysis model (HR=2.032, 95%CI=1.287-3.210, p=0.002). On comparing the recurrence site, marginally significant differences in hematological recurrence were noted between the PAR-high and PAR-low groups (50.0% *vs*. 21.6%, $p<0.001$).

A comparison of the postoperative clinical course between the PAR-low and PAR-high groups. The perioperative clinical course was similar between the PAR-low and PAR-high groups. The median postoperative hospital stay (42 days *vs*.

Table I. *Comparison of survival rates stratified by patient characteristics*.

Characteristics	No. of patients (%)	1-year OS rate (%)	3-year OS rate (%)	5-year OS rate (%)	*p*-Value
Age (years)					0.217
<70	92 (54.8%)	82.0	59.2	50.6	
≥70	76 (45.2%)	79.3	47.7	38.6	
Sex					0.712
Male	143 (85.1%)	80.2	52.0	43.7	
Female	25 (14.9%)	80.0	62.1	56.5	
Site of tumor					0.753
Upper	47 (28.0%)	76.2	53.8	50.4	
Middle	76 (45.2%)	79.7	48.8	44.8	
Lower	45 (26.8%)	85.3	63.1	41.1	
T status					<0.001
T1	67 (39.9%)	92.3	72.0	67.2	
T2 to T3	101 (60.1%)	72.3	43.0	32.3	
Lymph node metastasis					0.001
Negative	90 (53.6%)	84.9	65.2	60.1	
Positive	78 (46.4%)	74.8	42.1	29.8	
Platelet-albumin ratio					0.005
–<4,000	24	87.5%	70.4%	60.2%	
4,000<–<6,000	63	85.1%	57.3%	48.2%	
6,000<–<8,000	47	82.1%	58.5%	50.6%	
–>8,000	34	62.8%	30.2%	18.9%	
Lymphatic invasion					0.206
Negative	100 (59.5%)	80.3	59.7	53.6	
Positive	68 (40.5%)	79.9	46.8	35.2	
Vascular invasion					0.002
Negative	65 (38.7%)	85.4	68.4	59.3	
Positive	103 (61.3%)	76.8	45.4	36.9	
Postoperative surgical complications					0.988
No	121 (72.0%)	77.1	51.0	45.8	
Yes	47 (28.0%)	88.2	63.0	45.0	

OS: Overall survival.

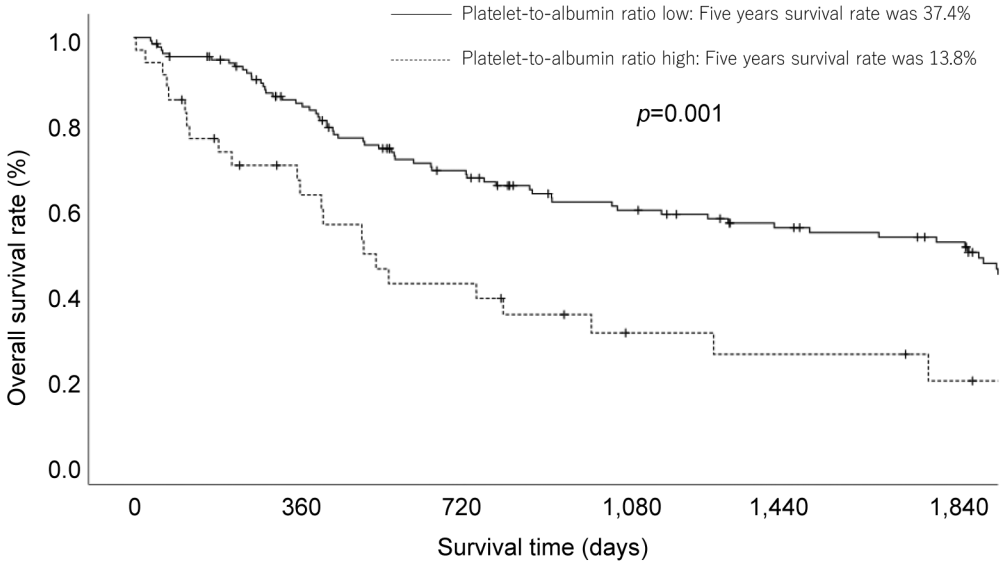

Figure 1. *A comparison of the overall survival in the platelet-to-albumin ratio (PAR)-high and PAR-low groups*.

Table II. *Uni- and multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.*

		Univariate analysis			Multivariate analysis		
Factors	No	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.218			
<70	92	1.000					
≥70	76	1.292	0.859-1.944				
Sex				0.712			
Female	25	1.000					
Male	143	1.117	0.621-2.011				
T status				<0.001			0.005
T1	67	1.000			1.000		
T2 or T3	101	2.450	1.539-3.900		2.030	1.240-3.323	
Lymph node metastasis				0.002			0.085
Negative	90	1.000			1.000		
Positive	78	1.922	1.275-2.897		1.464	0.948-2.261	
Platelet-albumin ratio				0.003			0.005
<8,000	134	1.000			1.000		
>8,000	34	1.394	1.120-1.734		1.997	1.230-3.241	
Lymphatic invasion				0.208			
Negative	100	1.000					
Positive	68	1.298	0.865-1.949				
Vascular invasion				0.002			
Negative	65	1.000					
Positive	103	2.021	1.291-3.163				
Tumor location				0.594			
Middle, lower	121	1.000					
Upper	47	1.135	0.713-1.807				
Postoperative complications				0.988			
No	121	1.000					
Yes	47	1.004	0.641-1.572				

45 days, p=0.749) and median operation time were similar between the PAR-low and PAR-high groups. In contrast, marginal but significant differences in the postoperative surgical complications and median intraoperative blood loss were noted between the groups. The incidence of postoperative surgical complications was 38.2% in the PAR-high group and 25.3% in the PAR-low group (p=0.136). Furthermore, the incidence of perioperative blood transfusion was significantly higher in the PAR-high group than in the PAR-low group (41.1% *vs*. 22.4%, p=0.026). The median intraoperative blood loss was 839 ml in the PAR-high group and 664 ml in the PAR-low group (p=0.172).

Discussion

The present study assessed whether the PAR has clinical impact on esophageal cancer patients who received curative treatment. The major finding was that the preoperative PAR did indeed affect the long-term oncological outcomes of esophageal cancer patients who received curative treatment. In addition, the perioperative PAR status also affected the short-term oncological outcomes. Therefore, our results suggest that the perioperative PAR is a promising prognostic factor for esophageal cancer patients.

In the present study, the 5-years OS rates were 51.7% in the PAR-low group and 18.9% in the PAR-high group. Furthermore, the HR of the PAR for the OS was 1.997. Similar results were observed in limited studies. Shirai *et al*. evaluated the prognostic value of the pretreatment PAR in 107 pancreatic cancer patients (14). They divided subjects into a PAR-low group (n=80) and PAR-high group (n=27) with a PAR cut-off value of 46.4×10^3. They demonstrated that the median OS was 77.1 months in the PAR-low group and 19.1 months in the PAR-high group. In addition, the median disease-free survival was 23.3 months in the PAR-low group and 8.5 months in the PAR-high group (p=0.003). They showed that a PAR-high status was a prognostic factor, and the HR of the PAR for OS was 1.971 (95%CI=1.128-3.444, p=0.017). Saito *et al*. investigated the clinical impact of the preoperative PAR in 59 cholangiocarcinoma patients (15). They divided subjects into a PAR-low group (n=43) and PAR-high group (n=16) at a PAR cut-off value of 72.6×10^3. They demonstrated that the 3-year OS was 93.1% in the PAR-low group and 49.3% in the PAR-high group. A PAR-high status was a prognostic factor, and the HR of the PAR for OS was 6.232

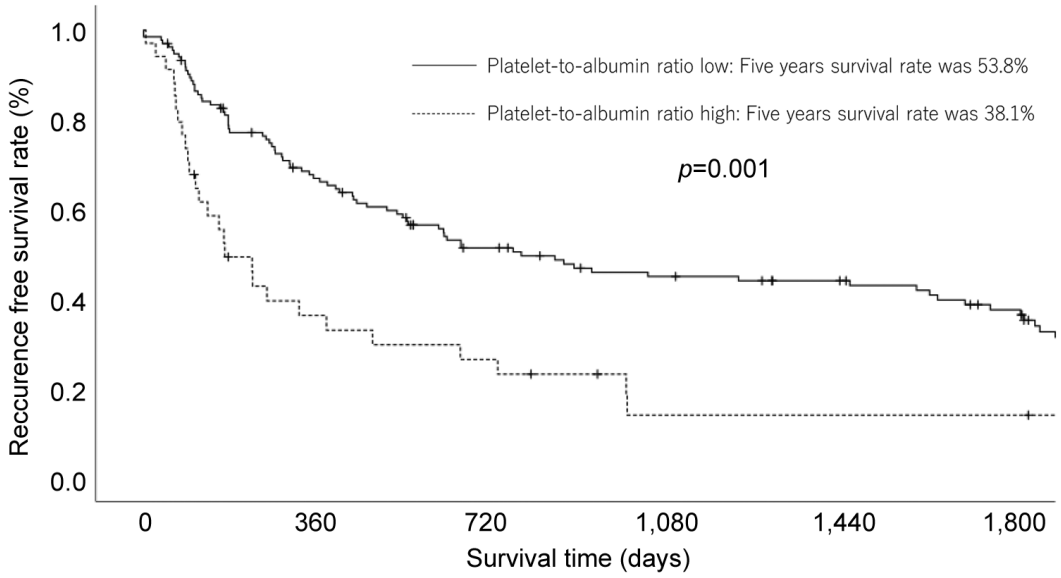

Figure 2. *A comparison of the recurrence-free survival in the platelet-to-albumin ratio (PAR)-high and PAR-low groups.*

Table III. *Uni- and multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence free survival.*

		Univariate analysis			Multivariate analysis		
Factors	No	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.647			
<70	92	1.000					
≥70	76	1.091	0.751-1.584				
Sex				0.431			
Female	25	1.000					
Male	143	1.237	0.728-2.101				
T status				<0.001			<0.001
T1	67	1.000			1.000		
T2 or T3	101	3.613	2.323-5.619		3.144	1.977-5.000	
Lymph node metastasis				<0.001			0.014
Negative	90	1.000			1.000		
Positive	78	2.278	1.564-3.318		1.643	1.105-2.445	
Platelet-albumin ratio				<0.001			0.002
<8,000	134	1.000			1.000		
>8,000	34	2.159	1.393-3.346		2.032	1.287-3.210	
Lymphatic invasion				0.014			
Negative	100	1.000					
Positive	68	1.593	1.100-2.307				
Vascular invasion				<0.001			
Negative	65	1.000					
Positive	103	2.565	1.678-3.922				
Tumor location				0.605			
Middle, lower	121	1.000					
Upper	47	1.118	0.732-1.707				
Postoperative complications				0.981			0.085
No	121	1.000			1.000		
Yes	47	1.005	0.664-1.552		1.469	0.949-2.275	

(95%CI=1.283-30.279, p=0.023). Li *et al*. clarified the clinical impact of the preoperative PAR in 628 hepatocellular carcinoma patients (16). They divided subjects into a PAR-low group (n=469) and PAR-high group (n=159) at a PAR cut-off value of 4.8. They demonstrated that the 5-year RFS was 47.3% in the PAR-low group and 26.1% in the PAR-high group. A PAR-high status was a prognostic factor, and the HR of the PAR for RFS was 1.700 (95%CI=1.332-2.171, p=0.001). In addition, the 5-year OS was 67.7% in the PAR-low group and 49.3% in the PAR-high group. A PAR-high status was a prognostic factor, and the HR of the PAR for OS was 1.778 (95%CI=1.291-2.449, p<0.001). Given these previous findings, the preoperative PAR appears to be a promising prognostic factor for esophageal cancer patients who receive curative treatment.

One possible reason why preoperative PAR affected the long-term oncological outcomes is that the preoperative PAR is related to the occurrence of postoperative surgical complications. In the present study, the occurrence of postoperative surgical complications was marginally but significantly higher in the PAR-high group than in the PAR-low group (38.2% *vs*. 25.3%, p=0.136). Recently, we reported that postoperative surgical complications were a significant prognostic factor for esophageal cancer patients (17-19). For example, we showed that postoperative pneumonia after esophagectomy was a prognostic factor for esophageal cancer patients. The 5-year OS was 55.1% in the non-pneumonia leakage group and 28.2% in the pneumonia group (p=0.006) (17). Therefore, the preoperative PAR might be associated with the occurrence of postoperative surgical complications. Another possible explanation is that the preoperative PAR is related to intraoperative blood transfusion. In the present study, the incidence of perioperative blood transfusion was significantly higher in the PAR-high group than that in the PAR-low group (41.1% *vs*. 22.4%, p=0.026). In addition, the amount of intraoperative blood loss was marginally but significantly higher in the PAR-high group than in the PAR-low group (839 ml *vs*. 664 ml, p=0.172). Perioperative blood transfusion and intraoperative blood loss have been shown to be prognostic factors in various malignancies, including esophageal cancer (20, 21). Therefore, preoperative PAR might be associated with the need for perioperative blood transfusion, and certain treatment strategies or postoperative management might be needed based on the preoperative PAR status.

Several suggestions for the future arise from the present study. First, there was some clinical relationship between the PAR and recurrence pattern. In the present study, the hematological recurrence rate was significantly higher in the PAR-high group than that in the PAR-low group. However, the optimal mechanism is unclear due to the fact that the PAR significantly affected the frequency of hematological recurrence. In addition, there have been no reports focusing on the relationship between the PAR and the recurrence pattern. Second, the optimal cut-off value of the PAR was unclear. In the present study, we set the cut-off value at 80×10^3 according to the 3- and 5-year OS rates. However, previous studies set other cut-off values for the PAR (14-17); for example, Shirai *et al*. set the cut-off value at 46.4×10^3 using a receiver operating characteristic (ROC) curve in 107 pancreatic cancer patients (14), and Saito *et al*. set the cut-off value at 72.6×10^3 using a ROC curve in 59 cholangiocarcinoma patients (15). In both instances, the PAR was calculated by dividing the platelet count (10^3/ml) by the serum albumin level (g/l). Ki *et al*. set the cut-off value at 4.8 using a ROC curve in 628 hepatocellular carcinoma patients (16), with the PAR calculated as the platelet count (10^9/l) divided by the serum albumin level (g/l). The differences in cut-off values were due to the number of patients, patients' background characteristics, and treatment strategies. To utilize the preoperative PAR for esophageal cancer treatment, it will be necessary to determine the optimal cut-off value. Further studies should be conducted focusing on this issue.

In conclusion, the preoperative PAR affected the long-term oncological outcomes of esophageal cancer patients who received curative treatment. Therefore, the perioperative PAR appears to be a promising prognostic factor for esophageal cancer patients.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TA, MJ, and KK made substantial contributions to the concept and design. TA, JM, SO, AO, AT, KK, KE, IH, HC, MF, HT, TO, NY, TO, and YR made substantial contributions to the acquisition of data and the analysis and interpretation of the data. TA, MJ, MN, HT, KH, NY, and YR were involved in drafting the article or revising it critically for important intellectual content. TA, MJ, KK, and YR gave their final approval of the version to be published.

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