Prognostic Significance of Combined Platelet Distribution Width and C-Reactive Protein Score in Esophageal Cancer

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Abstract. *Background/Aim:* The platelet distribution width (PDW) and serum C-reactive protein (CRP) levels are known to be predictive of prognosis in various malignancies. Our aim was to determine whether combining PDW and serum CRP levels produces a prognostic indicator for esophageal cancer (EC) patients. *Patients and Methods:* A total of 168 EC patients who underwent neoadjuvant therapy prior to esophagectomy were included in this study. *Results:* We defined a combined PDW and CRP (CPC) score as follows: patients with both low pretherapeutic PDW (≤ 12.4 fl) and high postoperative serum CRP levels (≥ 0.5 mg/dl) were assigned a score of 2, while patients with one or neither of those were assigned a score of 1 or 0. A multivariable analysis showed that the CPC score was a significant risk factor for overall ($p=0.006$) and recurrence-free ($p=0.004$) survival. *Conclusion:* The CPC score is a strong prognostic indicator in EC patients.

Esophageal cancer (EC) is highly invasive and metastatic, making it one of the most malignant of gastrointestinal tumors (1). Over the course of therapy, EC patients frequently exhibit hematological and serological abnormalities due to the burdens of adjuvant therapy, highly invasive esophagectomy, and postoperative complications (2, 3). In recent years, much effort has gone into establishing a novel prognostic marker for EC, analogous to the neutrophil-to-lymphocyte ratio (NLR) (4), by combining hematological and serological parameters obtained from routine blood tests. The platelet distribution width (PDW), a parameter determined from

complete blood count data, is a marker of the heterogeneity of platelet size and reflects platelet activity more directly than the mean platelet volume (MPV) (5, 6). Activated platelets are recognized to be key players in tumorigenesis (7), and high PDW levels are reportedly related to poor outcomes in various types of cancer (8-12). On the other hand, a small number of studies have demonstrated that low PDW levels are significantly associated with poor prognoses in gastric cancer (13, 14) and lung cancer (15, 16).

C-reactive protein (CRP) is one of the acute-phase proteins produced predominantly by hepatocytes in response to inflammation (17). Whether alone or combined with other routine blood data, elevated CRP levels have already been shown to be useful prognostic markers in several cancer types (18, 19). To the best of our knowledge, however, no studies have investigated whether combining PDW levels and serum CRP levels produces a stronger prognostic indicator of malignant tumors than other known prognostic markers. In the present study, therefore, we evaluated the predictive value of the combination of PDW levels and serum CRP levels for the survival of EC patients receiving neoadjuvant therapy (NAT) plus esophagectomy. In addition, we also determined at which point during the course of therapy each parameter correlated most strongly with prognosis.

Patients and Methods

Patients. This study was approved by the Ethics Committee of Akita University (Approval number: 547). It included 168 adult patients with cStage I-IVB EC who underwent NAT [21 neoadjuvant chemotherapy (NAC) and 147 NAC with radiotherapy (NACRT)] prior to esophagectomy at Akita University Hospital between September 2008 and December 2018. Cancer stage was classified according to the International Union Against Cancer tumor-node-metastasis (TNM) Classification of Malignant Tumors (8th edition) (20). Patients with Stage IVB had nonregional (lateral cervical) lymph node involvement but no distant organ metastasis. Informed consent for use of their clinical information in future medical research was obtained from all patients prior to surgery. The retrospective data were then collected for all patients at their initial visit (pretherapeutic time point), just before surgery

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(preoperative time point), and 2-3 months postoperatively (postoperative time point). In the measurement of hematological parameters, whole blood samples were collected in potassium ethylenediaminetetraacetic acid (EDTA)-containing tubes, and all samples were analysed within 30 min after blood collection using an automated hematological analyzer (Sysmex XS-800i, Kobe, Japan). Known prognostic markers, including the CRP to albumin ratio (CAR), controlling nutritional status (CONUT) score, lymphocyte-to-monocyte ratio (LMR), NLR, platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and the modified Glasgow prognostic score (mGPS), were also measured at the three time points. The formulas used to calculate the scores for these prognostic markers are described elsewhere (4, 21-26).

Treatment strategy. In general, patients with locally advanced or lymph node-positive tumors underwent NACRT. For NACRT, the radiotherapy consisted of 40-41.4 Gy in 20-23 fractions. For NAT, the chemotherapy consisted of continuous infusion of 5-fluorouracil (800 mg/m²/day) on days 1-5, combined with cisplatin or nedaplatin (80 mg/m²/day) on day 1. This protocol was repeated twice with 3- to 6-week intervals in between. Our standard operative procedure consisted of transthoracic esophagectomy or video-assisted thoracoscopic esophagectomy with two- (mainly for abdominal EC patients) or three-field lymphadenectomy and reconstruction with a gastric tube or pedicled colon through the posterior mediastinal or subcutaneous route (27).

Statistical analysis. Values are expressed as the median (interquartile range). Differences between two groups were analyzed using the Wilcoxon rank sum test for continuous variables and the Pearson χ^2 test or Fisher exact probability test for categorical variables. Survival length was determined from the date NAT was initiated to death or to the date of the last clinical follow-up. Survival curves were derived using the Kaplan–Meier method, and differences between the curves were assessed using the log-rank test (the Bonferroni-Holm correction was utilized for pairwise multiple comparisons). The hazard ratios for mortality were determined using Cox's proportional hazards regression models. Variables added in multivariable analyses were determined with stepwise regression. Statistical analyses were performed using JMP 14.2 (SAS Institute, Cary, NC, USA). Values of $p < 0.05$ (two-sided) were considered significant.

Results

Patient overview. The clinical characteristics of all patients included in this study are summarized in Table I. These patients included 145 (86.3%) males and 23 (13.7%) females with a median age of 64 years (range=59-68 years). Among the 168 patients, there were 6 (3.6%) with adenocarcinoma and 162 with squamous cell carcinoma (96.4%). The PDW levels at the pretherapeutic, preoperative, and postoperative time points were 11.1 (10.2-12.4) fl, 10.2 (9.1-11.2) fl, and 9.9 (8.9-10.9) fl, respectively, while serum CRP levels at the three time points were 0.13 (0.06-0.51) mg/dl, 0.14 (0.06-0.41) mg/dl, and 0.13 (0.05-0.46) mg/dl, respectively. Interestingly, the PDW levels in our cohort tended to be lower than in earlier studies of esophageal cancer (9, 10).

Overall survival and the PDW or serum CRP level at each time point. To assess the association between PDW at each time point and survival, we divided the patients into high and low groups using the respective upper quartile values for PDW at each time point as cut-off values. Patients with low pretherapeutic PDWs (≤ 12.4 fl, $n=126$) had significantly poorer prognoses than those with high pretherapeutic PDWs (> 12.4 fl, $n=42$) [5-year overall survival (OS): 60.6% vs. 75.3%, $p=0.044$, Figure 1a]. When we similarly divided the patients into two groups using the respective upper quartile values for serum CRP levels at each time point as cut-off values, we found that patients with high postoperative serum CRP levels (≥ 0.5 mg/dl, $n=49$) showed clearly poorer survival than those with low postoperative serum CRP levels (< 0.5 mg/dl, $n=119$) (5-year OS: 33.6% vs. 71.9%, $p < 0.001$, Figure 1f). Moreover, univariate analyses for 5-year OS revealed that low pretherapeutic PDW (≤ 12.4 fL) and high postoperative serum CRP levels (≥ 0.5 mg/dl) were significant prognostic factors [hazard ratio (HR)=2.130, 95% confidence interval (CI)=1.062-4.880, $p=0.049$ and HR=2.937, 95%CI=1.680-5.135, $p < 0.001$, respectively Figure 1a, f). On the other hand, we found no obvious differences in OS between two groups divided according to the respective cut-off values of PDW or CRP levels in other time points (Figure 1b, c, d, e).

Clinical characteristics of patients stratified according to CPC score. Based on the results summarized above, a combined PDW and CRP (CPC) score was calculated as follows: patients with both a low pretherapeutic PDW (≤ 12.4 fl) and high postoperative serum CRP levels (≥ 0.5 mg/dl) were assigned a score of 2, while patients with one or neither of those were assigned a score of 1 or 0. The clinicopathological features of the groups with each score are summarized in Table II. Regarding ypTNM staging, the score-2 group had more advanced tumor depth ($p=0.025$) and ypStage ($p=0.017$) than the other groups, and showed a lower rate of histological response to NAT (Grade 3) than the other groups ($p=0.002$). The score-2 group also had longer operation times ($p=0.010$), longer postoperative hospital stays ($p=0.035$), and greater intraoperative blood loss ($p=0.010$) than the other groups. In addition, the recurrence rate and the rate of cancer death were higher in the score-2 group than the other groups ($p=0.010$ and 0.004, respectively). For all other prognostic markers (CAR, CONUT, LMR, NLR, PLR, PNI and mGPS), the values exhibited by the score 2 group were poorer than those exhibited by the other groups.

Overall or recurrence-free survival and the CPC score. Using Kaplan–Meier analyses, the 5-year OS for the CPC score-0, score-1, and score-2 groups were 85.1%, 67.7%, and 26.8%, respectively (pairwise multiple comparison of the Kaplan–Meier curves: the score-0 vs. score-2 group,

Table I. Clinical characteristics of the patients (n=168).

	Median (IQR) or Number (%)
Age (years)	64 (59-68)
Gender, male/female	145 (86.3)/23 (13.7)
Pretherapeutic BMI (kg/m ²)	20.6 (18.7-23.2)
Tumor histology, AC/SCC	6 (3.6)/162 (96.4)
NAT, NAC or NACRT	21 (12.5)/147 (87.5)
Rate of NAT completion	148 (88.1)
NAT-induced adverse events (≥Grade 3)	86 (51.2)
Interval between NAT and esophagectomy (days)	37 (29-46)
Clinical tumor location, Upper/Middle/Lower	30 (17.9)/81 (48.2)/57 (33.9)
cT, T1/2/3/4a/4b	7 (4.2)/15 (8.9)/142 (84.5)/3 (1.8)/1 (0.6)
cN, N0/1/2/3	25 (14.9)/96 (57.1)/46 (27.3)/1 (0.6)
cM (nonregional lymph node involvement [†]), M0/1	149 (88.7)/19 (11.3)
cStage, I/II/III/IVA/IVB	6 (3.6)/32 (19.0)/106 (63.1)/6 (3.6)/18 (10.7)
ypT, T0/1/2/3/4a	46 (27.3)/28 (16.7)/20 (11.9)/67 (39.9)/7 (4.2)
ypN, N0/1/2/3	95 (56.5)/39 (23.2)/28 (16.7)/6 (3.6)
pM (nonregional lymph node involvement [†]), M0/1	154 (91.7)/14 (8.3)
ypStage, I/II/III/IVA/IVB	58 (34.5)/30 (17.9)/20 (11.9)/38 (22.6)/8 (4.8)/14 (8.3)
Tumor differentiation, G1/G2/G3	31 (18.5)/111 (66.1)/26 (15.5)
Histological response to NAT, Grade 1/2/3	64 (38.1)/70 (41.7)/34 (20.2)
Surgical approach, transthoracic/thoracoscopic	121 (72.0)/47 (28.0)
Lymph-node dissection, 2-fields/3-fields	7 (4.2)/161 (95.8)
Operation time (min)	571 (500-640)
Blood loss (ml)	553 (370-756)
Major complications (Clavien-Dindo ≥Grade IIIa)	
Overall	50 (29.8)
Anastomotic leakage	8 (4.8)
Pneumonitis	27 (16.1)
Recurrent nerve paralysis	16 (9.5)
Chylothorax	10 (6.0)
Postoperative mortality	2 (1.2)
Postoperative hospital stay (days)	28 (22-42)
Recurrence rate	63 (37.5)
Prognosis, alive /cancer death /death from other disease	113 (67.3)/46 (27.4)/9 (5.4)
Platelet, (×10 ⁴ /μl) pretherapeutic/preoperative/postoperative	24.4 (20.6-29.5)/20.4 (16.4-23.9)/20.9 (17.2-25.7)
lymphocyte, (/μl) pretherapeutic/preoperative/postoperative	1610 (1,330-1,947)/965 (722-1,317)/950 (770-1,270)
Neutrophil, (/μl) pretherapeutic/preoperative/postoperative	3820 (2,870-5,145)/2,335 (1,735-3,275)/2,830 (2,175-3,645)
Monocyte, (/μl) pretherapeutic/preoperative/postoperative	380 (300-460)/380 (280-480)/325 (240-427)
MPV, (fL) pretherapeutic/preoperative/postoperative	10.1 (9.4-10.6)/9.5 (9.0-10.0)/9.3 (8.8-9.9)
PDW, (fL) pretherapeutic/preoperative/postoperative	11.1 (10.2-12.4)/10.2 (9.1-11.2)/9.9 (8.9-10.9)
Albumin, (g/dl) pretherapeutic/preoperative/postoperative	4.0 (3.8-4.2)/3.8 (3.5-4.1)/3.9 (3.6-4.2)
CRP, (mg/dl) pretherapeutic/preoperative/postoperative	0.13 (0.06-0.51)/0.14 (0.06-0.41)/0.13 (0.05-0.46)
Total cholesterol, (mg/dl) pretherapeutic/preoperative/postoperative	185 (167-212)/201 (169-224)/185 (159-213)

[†]Lateral cervical lymph node involvement. IQR: Interquartile range; BMI: body mass index; AC: adenocarcinoma; SCC: squamous cell carcinoma; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; MPV: mean platelet volume; PDW: platelet distribution width; CRP: C-reactive protein.

$p < 0.001$; score-1 vs. score-2 group, $p < 0.001$; score-0 vs. score-1 group, $p = 0.279$) (Figure 2a). On the other hand, the 5-year recurrence-free survival (RFS) for the three groups were 74.8%, 59.4%, and 28.1%, respectively (pairwise multiple comparison of the Kaplan–Meier curves: the score-0 vs. score-2 group, $p < 0.001$; score-1 vs. score-2 group, $p = 0.001$; score-0 vs. score-1 group, $p = 0.311$) (Figure 2b). The score-0 group tended to show a better OS and RFS than

the score-1 group, though the difference between these two groups was not statistically significant.

Association between the CPC score and survival. We utilized Cox's proportional hazards regression models to further analyze the association between CPC scores and survival (Table III). For OS, the multivariable analysis showed that gender (HR=21.476, 95%CI=2.559-180.255, $p = 0.005$), pretherapeutic BMI

Figure 1. Kaplan–Meier and univariate Cox proportional hazards analyses of overall survival based on platelet distribution width (PDW) (a, b, c) and serum C-reactive protein (CRP) levels (d, e, f) at the indicated time points. HR: Hazard ratio; 95%CI: 95% confidence interval.

Table II. Clinical characteristics of the patients after stratification according to their CPC scores.

CPC score	Score-0 (n=30)	Score-1 (n=108)	Score-2 (n=30)	p-Value
Age, years (range)	65 (59-69)	63 (58-67)	64 (58-68)	0.563
Gender, male/female, n	25/5	91/17	29/1	0.189
Pretherapeutic BMI, kg/m ² (range)	21.4 (19.1-24.0)	20.8 (18.5-23.1)	19.5 (18.7-23.2)	0.291
NAT, NAC/NACRT, n	5/25	9/99	7/23	0.067
Rate of NAT completion, n (%)	28 (93.3)	94 (87.0)	26 (86.7)	0.619
NAT-induced adverse events (≥Grade 3), n (%)	10 (33.3)	58 (53.7)	18 (60.0)	0.081
Interval between NAT and esophagectomy, days (range)	37 (30-45)	36 (28-46)	43 (31-48)	0.397
Tumor location, Upper/Middle/Lower, n	7/14/9	19/52/37	4/15/11	0.897
cT, T1/2/3/4a/4b, n	2/5/23/0/0	4/9/92/3/0	1/1/27/3/1	0.247
cN, N0/1/2/3, n	8/13/9/0	15/67/25/1	2/16/12/0	0.183
cM (nonregional lymph node involvement [†]), M0/1, n	28/2	95/13	26/4	0.662
cStage I-II/III-IV, n	10/20	24/84	3/27	0.092
ypT, T0/1/2/3/4a, n	7/9/2/11/1	36/17/14/38/3	3/2/4/18/3	0.025
ypN, N0/1/2/3, n	22/7/1/0	62/22/20/4	11/10/7/2	0.077
pM (nonregional lymph node involvement [†]), M0/1, n	30/0	96/12	28/2	0.140
ypStage I-II/III-IV, n	21/9	57/51	10/20	0.017
Tumor differentiation, G1/G2/G3, n	7/17/6	20/72/16	4/22/4	0.740
Histological response to NAT, Grade 1/2/3, n	9/14/7	34/48/26	21/8/1	0.002
Surgical approach, transthoracic/thorascopic, n	21/9	79/29	21/9	0.190
Operation time, min (range)	562 (516-625)	563 (478-619)	637 (554-699)	0.010
Intraoperative blood loss, ml (range)	556 (301-789)	494 (331-707)	688 (541-812)	0.010
Complications (Clavien-Dindo ≥Grade IIIa), n (%)	6 (20.0)	31 (28.7)	13 (43.3)	0.131
Postoperative hospital stay, days (range)	28 (24-38)	26 (21-41)	31 (25-73)	0.035
Recurrence rate, n (%)	7 (23.3)	38 (35.2)	18 (60.0)	0.010
Prognosis, alive/cancer death /death from other disease, n	25/4/1	76/28/4	12/14/4	0.004
Pretherapeutic CAR (range)	0.028 (0.012-0.079)	0.032 (0.013-0.134)	0.059 (0.018-0.169)	0.536
Preoperative CAR (range)	0.044 (0.016-0.191)	0.035 (0.015-0.085)	0.041 (0.020-0.278)	0.407
Postoperative CAR (range)	0.015 (0.010-0.030)	0.026 (0.011-0.067)	0.331 (0.225-0.982)	<0.001
Pretherapeutic CONUT score (range)	1 (0-2)	1 (0-2)	1 (1-3)	0.338
Preoperative CONUT score (range)	2 (1-3)	3 (2-4)	4 (2-5)	0.048
Postoperative CONUT score (range)	2 (2-3)	2 (1-3)	3 (2-6)	0.002
Pretherapeutic LMR (range)	4.32 (3.26-5.89)	4.39 (3.23-5.80)	4.04 (3.24-5.44)	0.838
Preoperative LMR (range)	2.61 (1.86-4.17)	2.75 (1.93-3.67)	2.39 (1.92-3.49)	0.906
Postoperative LMR (range)	3.38 (2.24-4.88)	3.00 (2.41-4.71)	2.06 (1.41-3.81)	0.006
Pretherapeutic NLR (range)	2.30 (1.69-2.72)	2.40 (1.79-3.39)	2.48 (1.67-3.06)	0.540
Preoperative NLR (range)	2.28 (1.80-3.92)	2.56 (1.85-3.60)	3.04 (1.81-5.14)	0.570
Postoperative NLR (range)	2.76 (1.67-3.37)	2.65 (1.99-3.93)	3.62 (3.08-8.12)	0.009
Pretherapeutic PLR (range)	132 (100-168)	168 (127-198)	169 (129-205)	0.008
Preoperative PLR (range)	184 (120-281)	214 (169-270)	225 (161-357)	0.157
Postoperative PLR (range)	174 (137-211)	208 (158-294)	322 (212-409)	<0.001
Pretherapeutic PNI (range)	48.1 (45.3-52.3)	48.4 (44.6-52.6)	46.8 (43.9-50.2)	0.641
Preoperative PNI (range)	43.4 (39.8-46.2)	43.5 (40.1-46.1)	42.4 (38.4-45.5)	0.593
Postoperative PNI (range)	44.8 (41.3-48.3)	44.7 (41.5-48.1)	40.1 (35.3-43.8)	<0.001
Pretherapeutic mGPS, Score 0/1/2, n	28/1/1	92/9/7	24/5/1	0.387
Preoperative mGPS, Score 0/1/2, n	20/8/2	80/23/5	18/8/4	0.416
Postoperative mGPS, Score 0/1/2, n	25/5/0	93/12/3	8/13/9	<0.001

Statistically significant values ($p < 0.05$) are given in bold. [†]Lateral cervical lymph node involvement. CPC Score: Combined platelet distribution width and C-reactive protein score; BMI: body mass index; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; CAR: C-reactive protein-to-albumin ratio; CONUT score: controlling nutritional status score; LMR lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; mGPS: modified Glasgow prognostic score.

(HR=0.811, 95%CI=0.715-0.917, $p < 0.001$), ypN (HR=2.066, 95%CI=1.388-3.105, $p < 0.001$), CPC score (HR=2.639, 95%CI=1.327-5.322, $p = 0.006$), and postoperative NLR (HR=1.154, 95%CI=1.037-1.369, $p = 0.002$) were all independent

factors contributing to OS. In addition, the multivariable analysis revealed that ypN (HR=1.539, 95%CI=1.174-2.018, $p = 0.002$), ypM (HR=2.370, 95%CI=1.088-5.166, $p = 0.030$), the CPC score (HR=1.890, 95%CI=1.217-2.936, $p = 0.004$), and

Figure 2. Overall (a) and recurrence-free survival (b) stratified according to the CPC score. CPC score is an abbreviation for a combined platelet distribution width (PDW) and C-reactive protein (CRP) score and was defined as follows: patients with both low pretherapeutic PDW (≤ 12.4 fl) and high postoperative serum CRP levels (≥ 0.5 mg/dl) were assigned a score of 2, while patients with one or neither of those were assigned a score of 1 and 0.

preoperative mGPS (HR=1.506, 95%CI=1.032-2.198, $p=0.042$) were independent factors contributing to RFS.

Subgroup analysis stratified according to clinicopathological features. Kaplan–Meier subgroup analyses revealed that CPC scores correlated significantly with OS, regardless of whether patients were ypN-negative or -positive or ypStage I-II or III-VI (log rank $p=0.012$, 0.002, 0.007, and 0.004, respectively) (Figure 3). Moreover, the differences in OS between the score-0 and score-1 groups tended to be more remarkable among the patients with more advanced disease (node-positive or ypStage III-IV). The univariate analyses demonstrated that the CPC score was clearly related to OS, irrespective of age, tumor location, NAT, the presence or absence lymph node involvement, ypT or ypTNM Stage (Table IV).

Discussion

In this article, we showed for the first time that the combined pretherapeutic PDW and postoperative serum CRP levels produces a stronger predictor of prognosis in EC patients than other known prognostic markers. Although the CPC score reflected the ypTNM Stage of EC patients to some extent, the score-0 group included patients at more advanced Stages (ypStage III; 30% in the score-0 group), while the

score-2 group contained patients at less advanced Stages (ypStage I-II; total 33.3% in the score-2 group). Consequently, the advantage of the CPC score is that it enables detection of EC patients with favorable and poor prognoses, irrespective of ypTNM Stage.

Most studies of the association between PDW and malignancies have shown that high PDWs correlate significantly with poor prognoses (8-12). Within the tumor microenvironment, tumor cells induce platelet activation and aggregation, and enhance thrombopoiesis by releasing thrombopoietic cytokines, such as interleukin-6 (IL-6) and tumor-derived platelet factor 4 (PF4) (7). The activated platelets then release granules containing numerous tumor promoting factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF- β), which is followed by the release of extracellular vesicles (EVs) such as platelet-derived microparticles (PMPs) (7, 28). These various mediators then collectively act to facilitate tumor cell growth and proliferation, angiogenesis, and epithelial mesenchymal transition (EMT) (7, 28). The PDW is reported to more sensitively reflect variation in platelet volume related to pseudopodia formation and shape changes during platelet activation than MPV; consequently, elevated PDW is considered to be an indicator of platelet activation (6).

Table III. Univariate and multivariable analyses of survival (Cox's proportional hazards regression models).

Factor	OS			RFS		
	Univariate	Multivariable		Univariate	Multivariable	
	<i>p</i> -Value	Hazard ratio (95%CI)	<i>p</i> -Value	<i>p</i> -Value	Hazard ratio (95%CI)	<i>p</i> -Value
Age (years)*	0.796	—	—	0.168	—	—
Gender (male <i>vs.</i> female)	<0.001	21.476 (2.559-180.255)	0.005	0.235	—	—
Pretherapeutic BMI*	0.010	0.811 (0.715-0.917)	<0.001	0.120	—	—
cT (1, 2, 3, 4)*	0.063	—	—	0.025	1.186 (0.719-1.955)	0.504
cN (1, 2, 3)*	0.077	—	—	0.179	—	—
cM-nonregional lymph node involvement [†] (Yes <i>vs.</i> No)	0.247	—	—	0.181	1.186 (0.719-1.955)	—
ypT (0, 1, 2, 3, 4)*	0.003	1.027 (0.724-1.463)	0.882	<0.001	1.326 (0.969-1.814)	0.077
ypN (0, 1, 2, 3)*	<0.001	2.066 (1.388-3.105)	<0.001	<0.001	1.539 (1.174-2.018)	0.002
ypM-nonregional lymph node involvement [†] (Yes <i>vs.</i> No)	0.029	2.507 (0.907-6.932)	0.077	0.019	2.370 (1.088-5.166)	0.030
Tumor histology (SCC <i>vs.</i> AC)	0.856	—	—	0.724	—	—
Tumor differentiation (G1, 2, 3)*	0.992	—	—	0.717	—	—
NAT (NACRT <i>vs.</i> NAC)	0.530	—	—	0.522	—	—
Interval between NAT and surgery (≥37 days <i>vs.</i> ≤36 days)	0.629	—	—	0.172	—	—
NAT-induced adverse events (≥Grade 3) (Yes <i>vs.</i> No)	0.532	—	—	0.347	—	—
Histological response to NAT (Grade 1, 2, 3)*	<0.001	0.935 (0.460-1.878)	0.851	<0.001	1.020 (0.591-1.759)	0.943
Surgical approach (transthoracic <i>vs.</i> thorascopic)	0.988	—	—	0.683	—	—
Lymph node dissection (2-fields <i>vs.</i> 3-fields)	0.550	—	—	0.552	—	—
Mojoir Complication (Clavien-Dindo ≥IIIa) (Yes <i>vs.</i> No)	0.031	1.696 (0.865-3.326)	0.124	0.159	—	—
Perioperative blood transfusion (Yes <i>vs.</i> No)	0.184	—	—	0.492	—	—
CPC score*	<0.001	2.639 (1.327-5.322)	0.006	<0.001	1.890 (1.217-2.936)	0.004
Pretherapeutic MPV*	0.029	1.152 (0.722-1.846)	0.554	0.231	—	—
Pretherapeutic CAR*	0.032	1.771 (0.663-4.198)	0.237	0.200	—	—
Pretherapeutic CONUT*	0.360	—	—	0.420	—	—
Pretherapeutic LMR*	0.844	—	—	0.531	—	—
Pretherapeutic NLR*	0.467	—	—	0.469	—	—
Pretherapeutic PLR*	0.099	—	—	0.368	—	—
Pretherapeutic PNI*	0.120	—	—	0.793	—	—
Pretherapeutic mGPS*	0.083	—	—	0.571	—	—
Preoperative MPV*	0.361	—	—	0.434	—	—
Preoperative CAR*	0.234	—	—	0.056	—	—
Preoperative CONUT*	0.268	—	—	0.270	—	—
Preoperative LMR*	0.420	—	—	0.391	—	—
Preoperative NLR*	0.141	—	—	0.509	—	—
Preoperative PLR*	0.067	—	—	0.343	—	—
Preoperative PNI*	0.451	—	—	0.497	—	—
Preoperative mGPS*	0.015	1.003 (0.564-1.699)	0.993	0.021	1.506 (1.032-2.198)	0.042
Postoperative MPV*	0.301	—	—	0.945	—	—
Postoperative CAR*	0.005	0.872 (0.315-2.141)	0.788	0.270	—	—
Postoperative CONUT*	0.174	—	—	0.644	—	—
Postoperative LMR*	0.319	—	—	0.999	—	—
Postoperative NLR*	<0.001	1.154 (1.037-1.369)	0.002	0.107	—	—
Postoperative PLR*	0.647	—	—	0.991	—	—
Postoperative PNI*	0.127	—	—	0.825	—	—
Postoperative mGPS*	0.018	0.529 (0.241-1.072)	0.079	0.098	—	—

Statistically significant values ($p < 0.05$) are given in bold. *The hazard ratio for a one unit change; [†]Lateral cervical lymph node involvement. OS: Overall survival; RFS: recurrence-free survival; BMI: body mass index; AC: adenocarcinoma; SCC: squamous cell carcinoma; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; CPC score: combined platelet distribution width and C-reactive protein score; MPV: mean platelet volume; CAR: C-reactive protein-to-albumin ratio; CONUT score: controlling nutritional status score; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; mGPS: modified Glasgow prognostic score.

Figure 3. Subgroup analyses of overall survival based on CPC score stratified according to ypN negative or -positive and ypStage: ypN-negative (a), ypN-positive (b), ypStage I-II (c), and ypStage III-IV (d). CPC score is an abbreviation for a combined platelet distribution width (PDW) and C reactive protein (CRP) score and was defined as follows: patients with both low pretherapeutic PDW (≤ 12.4 fl) and high postoperative serum CRP levels (≥ 0.5 mg/dl) were assigned a score of 2, while patients with one or neither of those were assigned a score of 1 and 0.

By contrast, our findings indicate that low PDWs are related to poor outcomes, which is consistent with several earlier studies (13-16). Low MPV is reportedly predictive of unfavorable outcomes in diffuse large B-cell lymphoma (29), multiple myeloma (30), and lung cancer (31). Moreover, in

an analysis of 1544 patients with various types of cancer, Riedl *et al.* found that patients with high MPV levels exhibited both a lower risk of venous thromboembolism and better survival than those with lower MPV levels (32). These findings suggest that smaller platelets may have a stronger

Table IV. Subgroup univariate analyses of overall survival based on the CPC score (Cox's proportional hazards regression models).

Factor	N	Hazard ratio (95%CI)	p-Value
Age			
≤64	88	3.613 (1.860-7.092)	<0.001
≥65	80	2.410 (1.210-4.811)	0.012
Gender			
Male	145	2.695 (1.682-4.339)	<0.001
Female	23	2.236 (0.039-129.529)	0.711
Tumor location			
Upper	29	4.469 (1.159-17.759)	0.030
Middle or Lower	139	2.727 (1.636-4.560)	<0.001
Tumor differentiation			
G1-2	142	3.428 (2.056-5.740)	<0.001
G3	26	1.223 (0.270-4.663)	0.873
NAT			
NAC	21	3.617 (1.211-15.408)	0.020
NACRT	147	2.840 (1.645-4.889)	<0.001
Histological response to NAT			
Grade 1-2	134	2.660 (1.646-4.336)	<0.001
Grade 3	34	2.586 (0.324-21.731)	0.396
Tumor depth (T)			
cT1-2	23	5.154 (0.733-44.881)	0.100
cT3-4	145	2.741 (1.668-4.514)	<0.001
ypT0-2	88	2.618 (1.223-5.608)	0.013
ypT3-4	80	2.777 (1.483-5.244)	0.001
Lymph node involvement (N)			
cN0	25	1.197×10 ⁹ (2.355- –)	0.010
cN+	143	2.621 (1.594-4.318)	<0.001
ypN0	96	2.814 (1.338-5.927)	0.006
ypN+	72	2.562 (1.357-4.879)	0.004
Nonregional lymph node involvement [†] (M)			
cM0	149	2.805 (1.674-4.713)	<0.001
cM1	19	3.431 (0.930-13.152)	0.064
ypM0	154	3.074 (1.854-5.116)	<0.001
ypM1	14	2.469 (0.121-19.648)	0.473
TNM stage			
cStage I-II	37	6.431 (0.913-43.834)	0.062
cStage III-IV	131	2.556 (1.556-4.213)	<0.001
ypStage I-II	88	2.618 (1.223-5.608)	0.013
ypStage III-IV	80	2.778 (1.483-5.244)	0.001

Statistically significant values ($p < 0.05$) are given in bold. [†]Lateral cervical lymph node involvement. CPC score: combined platelet distribution width and C-reactive protein score; OS: overall survival; NAT: neoadjuvant therapy; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; TNM: tumor-node-metastasis.

prothrombotic tendency and may be more supportive of tumor development than larger platelets. Platelets with a low MPV also generally exhibit a low PDW. In our study, the patients with low PDWs, had MPVs nearly as low as the “low MPVs” defined in the studies mentioned above. In the present study, however, multivariable analysis showed no significant relation between MPV and survival, though a univariate analysis revealed that pretherapeutic MPV was a

significant indicator of OS. The role of platelets with a low PDW in tumor pathogenesis remains to be elucidated.

The PDW reportedly correlates with several inflammatory parameters (10). In the present study, however, the PDW only very weakly correlated with serum CRP levels at the pretherapeutic time point (data not shown). On the other hand, a low pretherapeutic PDW was a significant risk factor for cN- and ypN-positivity in the multiple logistic regression analysis [odds ratio=2.681 ($p=0.035$) and 2.458 ($p=0.029$), respectively]. These findings suggest that pretherapeutic PDW may reflect the magnitude of platelet-mediated cancer promotion in the tumor microenvironment that is not directly reflected as systemic inflammation.

The present study revealed that the pretherapeutic PDW is associated with survival, though neither the preoperative nor postoperative PDW reflected survival, which is consistent with several past studies (9, 12-16). One possible explanation for these results is that preoperative and postoperative PDWs are not affected by tumor progression alone, but also by other factors such as bone marrow suppression due to NAT and postoperative malnutrition arising from reduced oral intake of nutrition.

It is well known that chronic inflammation plays a crucial role in the development and progression of malignant tumors and that CRP is an important indicator of inflammation (17, 33-34). In the present study, the univariate analyses at the three time points showed that only serum CRP levels at the postoperative time point were positively associated with OS. One possible explanation for why postoperative serum CRP levels may be particularly important is that they directly reflect the magnitude of the chronic inflammation caused by the various stresses encountered by the patient during the course of therapy, especially those related to the surgical intervention and postoperative complications.

Lastly, there are two limitations to the present study. First, because of the small number of patients, we were unable to adequately assess the effect of the CPC score on survival among patients with adenocarcinoma and female patients. Second, due to the retrospective nature of this study, we could not fully verify the role of platelets with a low PDW in tumorigenesis. We will address these issues in the next study. Nonetheless, by combining pretherapeutic PDW and postoperative serum CRP levels, we have established a novel prognostic score that is predictive of outcomes in EC patients. This CPC score could potentially help clinicians assess EC patient prognosis, irrespective of ypTNM Stage.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare regarding this study.

Authors' Contributions

Guarantors of integrity of entire study and Study concepts: Kawakita Y; Study design or data acquisition or data analysis: Motoyama S, Sato Y, Wakita A, Nagaki Y, Imai K; Statistical analysis, and manuscript editing, Kawakita Y, Motoyama S, Minamiya Y.

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