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ORIGINAL ARTICLE

Mean platelet volume and platelet distribution width correlates with prognosis of early colon cancer

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Summary

Purpose: *Several platelet indices have been linked to prognosis of various cancers, including metastatic colorectal cancer. The aim of this study was to investigate the prognostic effect of mean platelet volume (MPV) and platelet distribution width (PDW) in early colon cancer (CC) patients.*

Methods: *This retrospective study included early CC patients who were followed up and treated between 2005 and 2017. Relapse free survival (RFS) and overall survival (OS) were determined with respect to several demographic and clinical characteristics of patients, including MPV and PDW. The cut-off value was determined as >8.5 fL for MPV (sensitivity: 67.1%, specificity 54.5%) and ≤16% for PDW (sensitivity: 66.7%, specificity: 60.0%).*

Results: *The study included 394 patients, 53.3% of which were male. Stage I, II, and III patients constituted 8.9%, 46.4%, and 44.7% of the study population, respectively. Among all patients, RFS and OS were significantly longer in patients with MPV≤8.5 fL and PDW>16 fL (p<0.001 and p=0.011 for MPV, respectively; and p<0.001 and p=0.026 for PDW, respectively). In patients with stage III disease, those with MPV≤8.5 fL had significantly longer RFS and OS compared to those with MPV >8.5 fL (p<0.001 and p=0.001, respectively). On the other hand, those with PDW>16% had significantly longer RFS than that in those with PDW ≤16 fL among stage III patients (p<0.001). In multivariate analysis, stage, perineural invasion, lymphovascular invasion, adjuvant treatment, CEA, CA19-9, PDW, and MPV were found the most significant factors affecting RFS.*

Conclusion: *Our study suggests that elevated MPV and decreased PDW appear to be unfavorable prognostic factors in early CC, especially in patients with stage III disease. Considering the wide availability and accessibility of these indices, it is reasonable to designate further larger prospective studies to clarify and verify their potential roles in early CC.*

Key words: *mean platelet volume, platelet distribution width, colon cancer, overal survival, relapse free survival*

Introduction

Colorectal cancer (CRC) is a common and lethal disease. It is the second most common cancer in men and the third most common cancer in women [1-3]. In early CRC, 5-year survival rates range from 58.3% to 82.7% [2]. The tumor-node-metastasis (TNM) stage system can predict the prognosis of CRC and many other cancers. Other factors such as microsatellite instability (MSI), the state of KRAS, NRAS, BRAF, and tumor location are also predictive factors for CRC prognosis [4-8].

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Inflammation has a significant role in tumor progression and metastasis. Platelets play an important role in inflammation [9]. Activated platelets promote cancer cell growth, angiogenesis, and invasion [10]. Some platelet indices are related with prognosis of various cancers, including non-small cell lung cancer, breast cancer, gastric cancer, CRC, pancreatic cancer, and laryngeal cancer. These include total platelet count (TPC), mean platelet volume (MPV), and platelet distribution width (PDW), which can be easily tested [11-13].

MPV is a platelet volume index. Larger platelets (i.e., high MPV value) are more reactive than smaller ones as they can more easily release chemical mediators in response to inflammation [14]. This might explain why MPV was correlated with various thromboembolic disorders and pathophysiological characteristics of various disorders [15]. On the other hand, PDW is an indicator of variation in platelet size [16]. However, the specific mechanism by which PDW affect cancer progression is unclear. Malfunction of megakaryocytes may be related to the decreased PDW [17].

The aim of this study was to investigate the prognostic effect of MPV and PDW in early colon cancer (CC) patients.

Methods

Patients

This retrospectivety study included patients who were followed up and treated in the oncology clinic between 2005 and 2017. Patients with pathologically diagnosed CC, who had no metastasis, were included in the study. Staging of disease was performed according to computed tomography (CT), positron emission tomography-CT (PET-CT), and magnetic resonance imaging (MRI) findings before surgical treatment. Patients with diagnosis of rectal cancer, malignancy out of the the colon, presence of metastasis, hematological or autoimmune disease, those using aspirin, under <18 years of ages, and patients with missing data were excluded. In our hospital, all patients eligible for surgery are postoperatively referred to the medical oncology department in order to assess whether they require adjuvant treatment. Ensuring 10-12 h of fasting, samples for blood tests are routinely taken from antecubital vein by establishing mild venous stasis at upper arm in patients who apply to oncology clinic before treatment. Blood samples for biochemical parameters are taken into the anticoagulant-free gel tubes and those for complete blood counts into ethylenediamine tetraacetate-containing tubes. Complete blood count parameters are examined in hemogram autoanalyser (Mindray, China). Biochemical parameters are tested in autoanalyser (Beckman Coulter, USA) using colorimetric method. Based on the stage and risk stratification, patients received adjuvant therapy as capecitabine or 5-fluorouracil (FU) plus leucovorin (FULV), CAPOX (capecitabine+oxaliplatin), or modified 5-fluorouracil + leukovorin + oxaliplatin (mFOLFOX). Clinical, pathological, and laboratory data of all patients who were diagnosed with CC and who applied to the medical oncology outpatient clinic, were recorded.

Data collection

Medical records were reviewed to collect data about the age, gender, alcohol use, smoking, initial presentation, presence of obstruction/perforation,

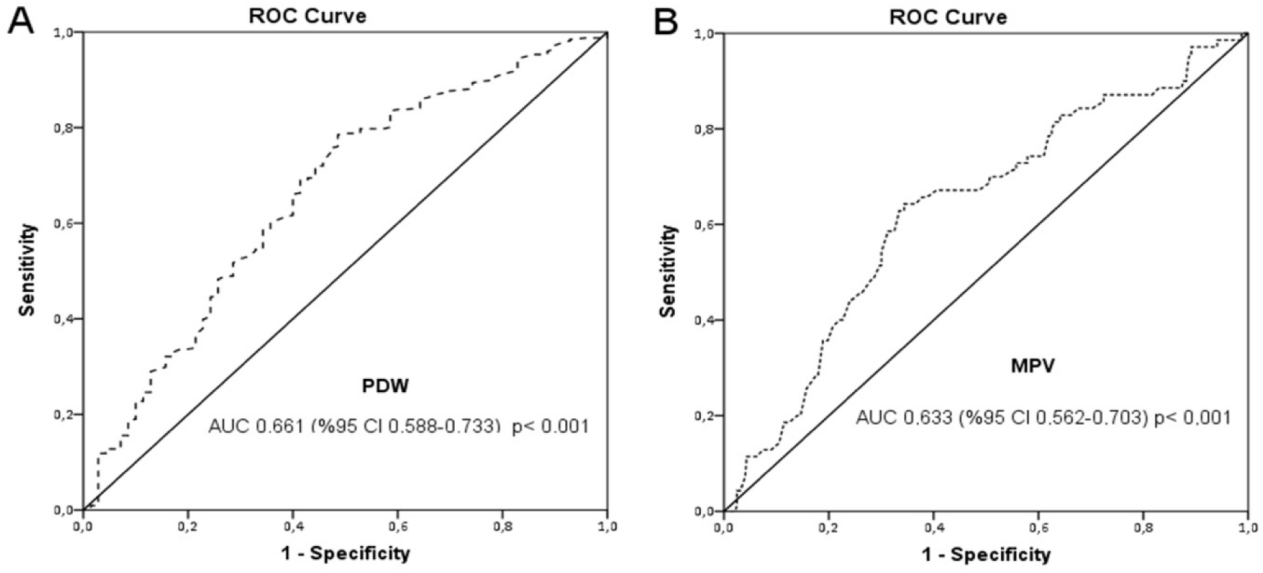

Figure 1. Receiver operating characteristic curve analyses for RFS: **(A)** PDW is represented by the line with an AUC=0.661 (95% CI, 0.588–0.733, p<0.001) with a sensitivity of 66.7% and a specificity of 60.0%, and **(B)** MPV is represented by the line with an AUC=0.633 (95% CI, 0.562–0.703, p<0.001) with a sensitivity of 67.1% and a specificity of 59.1%. AUC: area under the curve; CI: confidence interval; MPV: mean platelet volume; PDW: platelet distribution width; RFS: relapse-free survival.

concomitant diabetes mellitus (DM) or hypertension (HT), histological features (adenocarcinoma, mucinous adenocarcinoma), grade, primary tumor localization, stage, perineural invasion (PNI), lymphovascular invasion (LVI), surgical margin positivity, adjuvant treatment regimen, and final status (dead-alive) of patients. Likewise, patients with carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), white blood cell (WBC), hematocrit (Hct), hemoglobin (Hb), mean corpuscular volume (MCV), total platelet count (TPC), red blood cell distribution width (RDW), MPV, PDW, total neutrophil count (TNC), total lymphocyte count (TLC), and total monocyte count (TMC) at baseline were assessed to check the appropriateness of postoperative adjuvant treatment. Receiver operating characteristic (ROC) curves were plotted for MPV and PDW values for relapse-free survival (RFS). The area under the curve (AUC) was 0.633 (95% CI, 0.562-0.703, p<0.001) and AUC=0.661 (95% CI, 0.588-0.733, p <0.001), respectively. The cut-off for MPV was found as >8.5 fL with sensitivity of 67.1% and specificity of 54.5%. The cut-off for PDW was found as ≤16 fL with 66.7% sensitivity and 60.0% specificity (Figure 1). Patients were stratified by age (<65 years vs. ≥ 65 years), grade (1+2 vs. 3), and stage (I+II vs. III). Further stratification included MPV as being ≤8.5 fL or >8.5 fL and PDW as being ≤16% or >16%. Overall survival (OS) was calculated as the time elapsed from the diagnosis till death or the last visit. Disease-free survival (DFS) was defined as the time from curative surgery to local or distant recurrence.

Statistics

SPSS 22.0 for Windows software was used for the statistical analysis. Descriptive statistics were presented as mean, standard deviation, minimum, and maximum values for numerical variables; and as number and percentage for categorical variables. Numerical variables between two independent groups were analyzed with Student's t-test in case of normal distribution and with Mann Whitney U test if else. Categorical variables were compared between the groups by chi-square analysis. Monte Carlo simulation was applied if conditions could not be met. Survival analyses were performed with Kaplan-Meier analysis and compared with log rank thest. Determinant factors were examined with Cox regression analysis. Backward stepwise model was used with parameters having a p value below 0.10. Cut-off value was determined with ROC curve analysis. An overall 5% alpha error level was used to infer statistical significance.

Ethical approval

The study was performed in accordance with the declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital (48670771-514.10).

Results

The study included 394 patients, 53.3% of which were male. The median age of the patients was 60 years (range: 22-90), and 146 (37.1%) patients were ≥65 years old. Thirty-seven (9.4%) patients were regular alcohol users and 37.1% had history of smoking. About 14.7% of the patients presented with obstruction/perforation. There were 48 (12.2%) patients with DM and 123 (31.2%) patients with HT.

Fifty-eight (14.7%) patients had mucinous adenocarcinoma. More than half (54.3%) of patients' tumors were localized to the left colon. Stage I, II, and III patients constituted 8.9%, 46.4%, and 44.7% of the study population, respectively. About a quarter of patients (24.4%) had PNI and over one-third (35.3%) had LVI. Four (1%) patients had positive surgical margins. One-fifth of patients (20.6%) did not receive adjuvant treatment. Median follow-up was 78.5 months, during which 70 (17.8%) patients had recurrence and 44 (11.2%) patients died. There was no statistically significant difference between each of the MPV and PDW strata in terms of age, gender, smoking, alcohol use, obstruction/perforation, DM, HT, grade, primary tumor localization, stage, surgical margin positivity, adjuvant treatment use, and mortality (Table 1).

In the group with PDW ≤16%, the rate of mucinous adenocarcinoma was statistically higher than that in the group with PDW >16% (p=0.005). PNI was significantly more common in group with PDW ≤16% than that in those with PDW >16%. Likewise, PNI was greater in group with MPV >8.5 fL than that in those with MPV ≤8.5 fL (p=0.001 and p=0.003, respectively). LVI was significantly more common in the PDW ≤16% group than that in the PDW >16% group (p=0.001). There were statistically significant differences between the groups in terms of the adjuvant regimens (p<0.001). The recurrence rates were significantly higher in those with PDW ≤16% compared to those with PDW >16% (p<0.001). Similarly, recurrence rates were more common in those with MPV >8.5 fL compared to those with MPV ≤8.5 fL (p<0.001), (Table1).

The study groups, which were stratified by either MPV or PDW, did not differ in terms of median CA19-9, AST, ALT, GGT, WBC, Hct, Hgb, MCV, RDW, TNC, and TLC. Median CEA was significantly higher in the PDW ≤16 % group compared to those with PDW >16% (p=0.026). Median creatinine was statistically higher in the group with PDW >16% than that in those with PDW ≤16% (p<0.001). Likewise, median creatinine was higher in the group with MPV ≤8.5 fL compared to those with MPV >8.5 fL (p=0.031). Median albumin was

Table 1. The characteristics of patients according to PDW and MPV groups

Variables	*All patiens (n=394) n (%)*	*PDW ≤16 (n=152) n (%)*	*PDW >16 (n=242) n (%)*	*p*	*MPV ≤8.5 (fL) (n=216) n (%)*	*MPV >8.5 (fL) (n=178) n (%)*	*p*
Age (years)							
Median, years (min-max)	60 (22-90)	60 (22-90)	60 (25-90)	0.754	59 (22-84)	61 (25-90)	0.376
<65	248 (62.9)	95 (62.5)	153 (63.2)	0.885	141 (65.3)	107 (60.1)	0.291
≥65	146 (37.1)	57 (37.5)	89 (36.8)		75 (34.7)	71 (39.9)	
Gender							
Male	210 (53.3)	85 (55.9)	125 (51.7)	0.408	112 (51.9)	98 (55.1)	0.526
Female	184 (46.7)	67 (44.1)	117 (48.3)		104 (48.1)	80 (44.9)	
Alcohol use	37 (9.4)	19 (12.5)	18 (7.4)	0.094	21 (9.7)	16 (9.0)	0.863
Smoking	146 (37.1)	49 (32.2)	97 (40.1)	0.116	87 (40.3)	59 (33.1)	0.145
Obstruction/perforation	58 (14.7)	28 (18.4)	30 (12.4)	0.100	28 (13.0)	30 (16.9)	0.278
DM	48 (12.2)	16 (10.5)	32 (13.2)	0.426	27 (12.5)	21 (11.8)	0.832
HT	123 (31.2)	46 (30.3)	77 (31.8)	0.746	72 (33.3)	51 (28.7)	0.318
Tumor histology							
AC	336 (85.3)	120 (78.9)	216 (89.3)	**0.005**	189 (87.5)	147 (82.6)	0.171
Mucinous AC	58 (14.7)	32 (21.1)	26 (10.7)		27 (12.5)	31 (17.4)	
Grade							
Well/moderately	370 (93.9)	140 (92.1)	230 (95)	0.236	207 (95.8)	163 (91.6)	0.092
Poorly	24 (6.1)	12 (7.9)	12 (5)		9 (4.2)	15 (8.4)	
Tumor localization							
Right colon	180 (45.7)	64 (42.1)	116 (47.9)	0.258	98 (45.4)	82 (46.1)	0.890
Left colon	214 (54.3)	88 (57.9)	126 (52.1)		118 (54.6)	96 (53.9)	
Stage							
I	35 (8.9)	9 (5.9)	26 (10.7)	0.061	21 (9.7)	14 (7.9)	0.222
II	183 (46.4)	65 (42.8)	118 (48.8)		107 (49.5)	76 (42.7)	
III	176 (44.7)	78 (51.3)	98 (40.5)		88 (40.7)	88 (49.4)	
PNI positivity	96 (24.4)	51 (33.6)	45 (18.6)	**0.001**	40 (18.5)	56 (31.5)	**0.003**
LVI positivity	139 (35.3)	69 (45.4)	70 (28.9)	**0.001**	67 (31.0)	72 (40.4)	**0.051**
Surgical margin positivity	4 (1.0)	2 (1.3)	2 (0.8)	0.637	2 (0.9)	2 (1.1)	0.846
Adjuvant treatment							
No	81 (20.6)	25 (16.4)	56 (23.1)	0.110	47 (21.8)	34 (19.1)	0.516
Yes	313 (79.4)	127 (83.6)	186 (76.9)		169 (78.2)	144 (80.9)	
Adjuvant regimen							
mFOLFOX	74 (23.3	36 (28.3)	38 (20.0)	**<0.001**	35 (20.5)	39 (26.7)	**<0.001**
CAPOX	47 (14.8)	30 (23.6)	17 (8.9)		16 (9.4)	31 (21.2	
FULV	183 (57.7)	49 (38.6)	134 (70.5)		118 (69.0)	65 (44.5)	
Capecitabine	13 (4.1)	12 (9.4)	1 (0.5)		2 (1.2)	11 (7.5)	
Recurrence							
Yes	70 (17.8)	42 (27.6)	28 (11.6)	**<0.001**	23 (10.6)	47 (26.4)	**<0.001**
Locoregional	23 (32.9)	13 (31.0)	10 (35.7)	0.678	8 (34.8)	15 (31.9)	0.810
Systemic	47 (67.1)	29 (69.0)	18 (64.3)		15 (31.9)	32 (68.1)	
Metastasectomy	20 (28.6)	11 (26.2)	9 (32.1)	0.589	7 (30.4)	13 (27.7)	0.809
Final Status							
Deceased	44 (11.2)	18 (11.8)	26 (10.7)	0.736	21 (9.7)	23 (12.9)	0.316
Alive	350 (88.8)	134 (88.2)	216 (89.3)		195 (90.3)	155 (87.1)	

AC: adenocarcinoma; CAPOX: capecitabine plus oxaliplatin; DM: Diabetes mellitus; FULV: fluorouracil plus leucovorin; HT: hypertension; LN: lymph node; LVI: lymphovascular invasion; mFOLFOX: modified fluorouracil plus leucovorin plus oxaliplatin; MPV: mean platelet volume; PDW: platelet distribution width; PNI: perineural invasion.
Bold numbers denote statistical significance.

significantly higher in PDW ≤16% group compared to those with PDW >16% (p=0.040). Similarly, it was greater in MPV >8.5 fL group than that in those with MPV ≤8.5 fL (p<0.001). Median LDH was significantly higher in those with PDW >16% compared to those with PDW ≤16% (p=0.044). Median TPC was significantly higher in the group with MPV ≤ 8.5 fL compared to that in those with MPV >8.5 fL (p<0.001). Median TMC were significantly higher in the group with PDW ≤16% than that in those with PDW >16% (p<0.001) (Table 2).

RFS rates at 12, 36, 60, and 120 months were 95.7%, 86.7%, 84% and 80.8% in the general study population, respectively. The corresponding OS rates were 99.2%, 95.5%, 90.4%, and 83.2%, respec-

Table 2. Laboratory data of patients according to PDW and MPV groups

Variables	*All patients (n=394) Median (min-max)*	*PDW ≤16 (n=152) Median (min-max)*	*PDW>16 (n=242) Median (min-max)*	*p*	*MPV ≤8.5 (fL) (n=216) Median (min-max)*	*MPV >8.5 (fL) (n=178) Median (min-max)*	*p*
CEA, ng/mL	1.73 (0.2-12.0)	1.90 (0.4-11.5)	1.66 (0.2-10.9)	**0.026**	1.64 (0.2-12.0)	1.90 (0.4-11.6)	0.054
CA19:9, U/mL	10.0 (0.6-32.0)	12.0 (0.6-31.0)	9.30 (0.80-32.3)	0.100	9.0 (0.80-30.5)	11.70 (0.6-28.9)	0.064
Creatinin, mg/dL	0.81 (0.2-3.0)	0.80 (0.38-1.99)	0.90 (0.20-3.0)	**<0.001**	0.86 (0.46-2.50)	0.81 (0.20-3.0)	**0.031**
AST, U/L	19.0 (1.2-628)	19.0 (5.0-74.0)	19.0 (1.2-628.0)	0.205	19.0 (1.2-140.0)	20.0 (4.0-628.0)	0.789
ALT, U/L	19.0 (2-556)	18.0 (5.0-113.0)	19.0 (2.0-556.0)	0.539	19.0 (2.0-206.0)	18.0 (5.0-556.0)	0.429
ALP, U/L	85.50 (9-870)	85.0 (10.0-870.0)	86.0 (8.0-429.0)	0.519	87.50 (9.0-870.0)	83.0 (10.0-429.0)	0.170
GGT, U/L	32.50 (3.8-463)	27.0 (7.0-303.0)	33.0 (3.8-463.0)	0.407	34.0 (3.8-448.0)	27.0 (7.0-463.0)	0.059
Albumin, g/dL	4.10 (2.6-5.04)	4.22 (3.0-5.04)	4.10 (2.60-4.80)	**0.040**	4.0 (2.6-4.6)	4.21 (3.0-5.04)	**<0.001**
LDH, U/L	188.0 (76.0-819.0)	184.0 (111.0-819.0)	196.0 (76.0-735.0)	**0.044**	196.0 (76.0-735.0)	185.0 (112.0-819.0)	**0.063**
WBC, 10^3/UL	7.2 (2.5-17.8)	7.2 (2.5-17.8)	7.2 (3.8-16.6)	0.982	7.2 (3.9-17.8)	7.1 (2.5-16.5)	0.561
Hct, %	35.5 (2.0-50.0)	36.0 (26.0-50.0)	35.0 (23.0-50.0)	0.988	35.0 (23.0-47.0)	36.0 (24.0-50.0)	0.060
Hb, g/dL	11.9 (6.1-16.9)	11.8 (6.20-16.8)	11.9 (6.1-16.9)	0.292	11.7 (6.1-16.2)	12.1 (8.2-16.9)	0.134
MCV, fL	82.6 (65-102)	82.9 (10.50-10.0)	82.6 (7.50-102.08)	0.605	82.2 (7.5-10.08)	83.4 (8.8-10.0)	0.563
TPC, 10^3/UL	291.0 (77.5-954)	308.5 (91.0-763.0)	283.5 (77.5-957.0)	0.651	332.0 (77.5-954.0)	272.0 (91.0-738.0)	**<0.001**
RDW, %	15.6 (11.6-33.3)	15.7 (11.9-27.0)	15.6 (11.6-33.3)	0.799	15.6 (11.6-31.6)	15.70 (11.9-33.3)	0.721
MPV, fL	8.3 (5.4-13.0)	9.6 (5.9-13.0)	7.8 (5.4-11.6)	**<0.001**	7.5 (5.4-8.5)	9.6 (8.6-13.0)	**<0.001**
PDW, %	16.3 (8.4-65.4)	13.0 (8.4-16.0)	16.8 (8.4-65.4)	**<0.001**	16.6 (8.4-62.9)	14.3 (8.4-65.4)	**<0.001**
TNC, 10^3/UL	4.2 (1.0-14.0)	4.1 (1.30-14.0)	4.2 (1.0-14.0)	0.231	4.3 (1.0-14.0)	4.1 (1.3-11.0)	0.082
TLC, 10^3/UL	2.0 (0.5-7.7)	2.0 (0.5-7.7)	2.0 (0.6-5.9)	0.469	2.0 (0.6-5.1)	2.0 (0.54-7.7)	0.404
TMC, 10^3/UL	0.5 (0.1-1.7)	0.5 (0.2-1.7)	0.4 (0.1-1.3)	**<0.001**	0.4 (0.1-1.7)	0.5 (0.2-1.4)	**0.012**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryogenic antigen; Hb: hemoglobin; Hct: hematocrit; GGT: gamma glutamyl transferase; IQR: interquartile range; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; MPV: mean platelet volume; PDW: platelet distribution width; RDW: red blood cell distribution width; TLC: total lymphocyte count; TMC: total monocyte count; TNC: total neutrophil count; TPC: total platelet count; WBC: white blood cells.
Bold numbers denote statistical significance.

Table 3. Relapse-free and overall survival rates at 12, 36, 60, and 120 months in PDW and MVP groups

RFS (months)	*All patients (%)*	*PDW≤ 16% (%)*	*PDW> 16% (%)*	*MPV ≤8.5 fL (%)*	*MPV >8.5 fL (%)*
12	95.7	92.8	98.3	98.6	94.4
36	86.7	73.5	93.8	94.4	76
60	84	72.3	91.3	93	72.1
120	80.8	70.2	87.7	89	70.5
OS (months)	*All patients (%)*	*PDW≤ 16% (%)*	*PDW> 16% (%)*	*MPV ≤8.5 fL (%)*	*MPV >8.5 fL (%)*
12	99.2	99.3	99.2	99.1	99.4
36	95.5	92.22	97.1	97.2	93.1
60	90.4	87.4	92	93.9	84.2
120	83.2	74.6	86.1	87.6	75.2

MPV: mean platelet volume; OS: overall survival; PDW: platelet distribution width; RFS: relapse-free survival

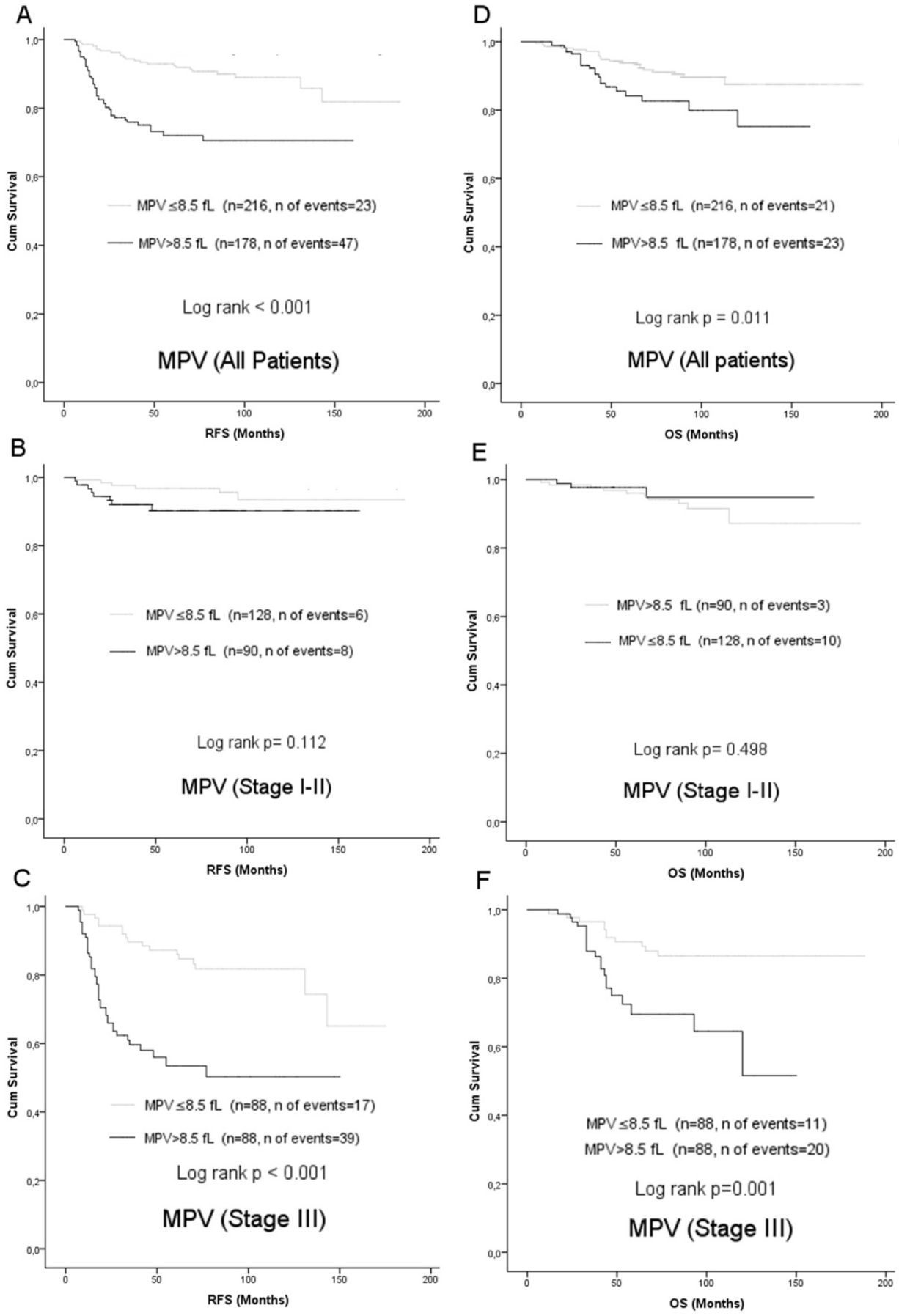

Figure 2. Kaplan–Meier plot of RFS and OS stratified by the mean platelet volume. MPV: mean platelet volume; OS: overall survival; PDW: platelet distribution width; RFS: relapse-free survival.

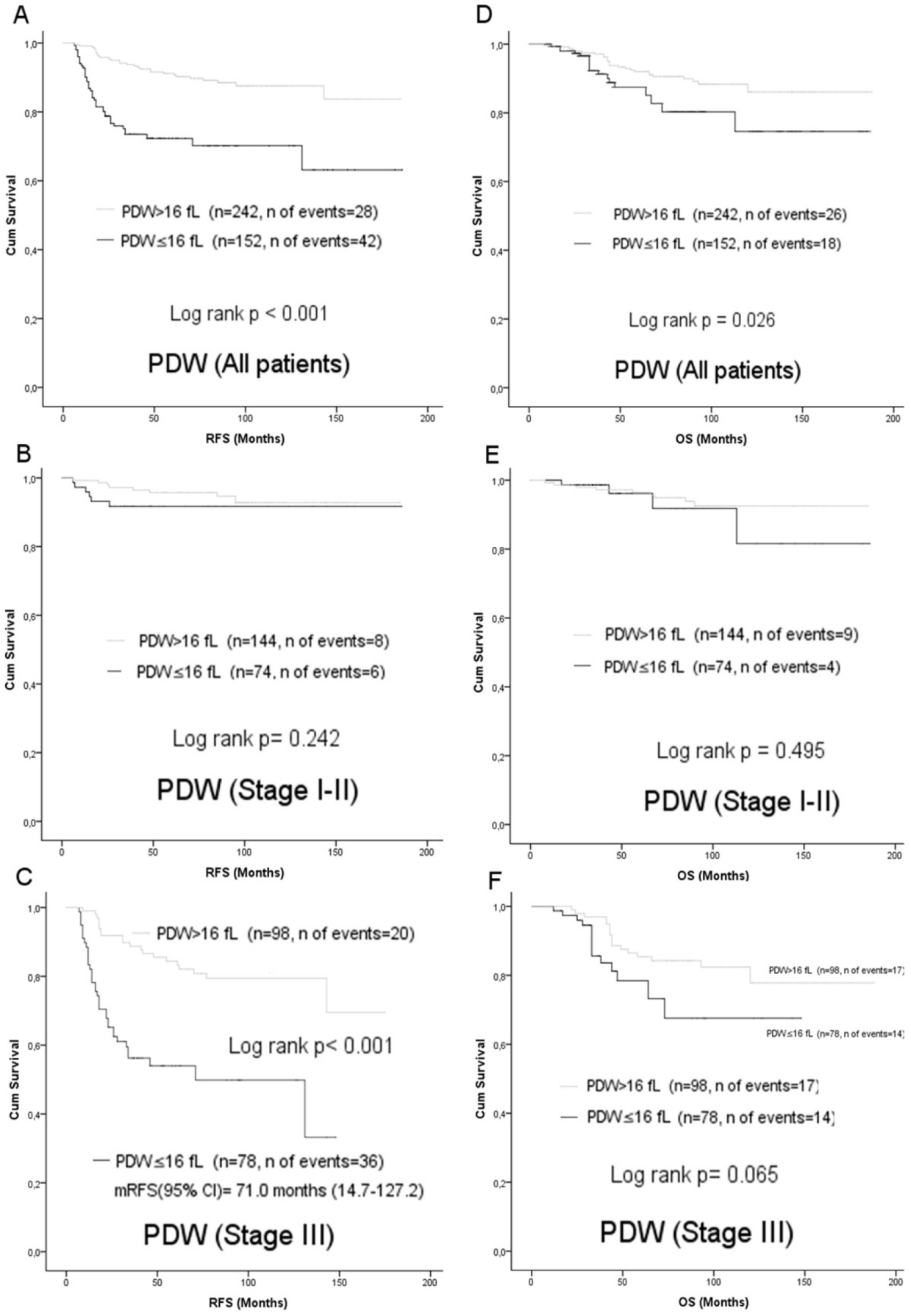

Figure 3. Kaplan–Meier plot of RFS and OS stratified by the pre-treatment platelet distribution width. MPV: mean platelet volume; OS: overall survival; PDW: platelet distribution width; RFS: relapse-free survival.

tively. The survival rates at 12, 36, 60, and 120 months are summarized in Table 3.

Kaplan-Meier analysis showed significantly increased RFS and OS for those having MPV ≤8.5 fL compared to those having MPV >8.5 fL (log rank p<0.001 and log rank p=0.011 respectively). Such comparison by stages revealed no difference between MPV groups in terms of RFS or OS among those with stage I or II disease (log rank p=0.112 and log rank p=0.498, respectively), whereas those with MPV >8.5 fL and stage III disease had significantly shorter RFS and OS (log rank p<0.001 and log rank p=0.001, respectively) (Figure 2).

The comparison between PDW groups showed significantly longer RFS and OS in patients with PDW >16% compared to those with PDW ≤16% (log rank p<0.001 and log rank p=0.026, respectively) Among patients having stage I or II disease, PDW groups did not differ with respect to RFS or OS (log rank p=0.242 and log rank p=0.495, respectively). On the other hand, stage III patients with PDW>16% had significantly longer RFS than that in stage III patients with PDW ≤16 fL (log rank p<0.001). In stage III, while median RFS was not reached in patients who had PDW >16%, it was detected as 71.0 months (95% CI, 14.7-127.2) in those with PDW ≤16%. PDW groups at stage III disease did not differ in terms of OS (log rank p=0.065) (Figure 3).

In univariate analysis, obstruction/perforation, grade, stage, PNI, LVI, adjuvant treatment, CEA, CA19-9, PDW, MPV, and TMC were the statistically significant prognostic factors for RFS (p=0.012, p=0.003, p<0.001, p<0.001, p<0.001, p=0.001, p<0.001, p=0.005, p<0.001, p<0.001, and p=0.034, respectively). The multivariate analysis showed that the stage, PNI, LVI, adjuvant treatment, CEA, CA19-9, PDW, and MPV as the most significant factors for RFS (p<0.001, p<0.001, p=0.042, p=0.036, p=0.031, p=0.007, p=0.002, and p=0.017, respectively) (Table 4).

The univariate analysis for OS revealed that age, DM, HT, stage, PNI, LVI, recurrence, CEA, CA19-9, PDW, and MPV (p=0.002, p=0.005, p=0.020, p<0.001, p<0.001, p<0.001, p<0.001, p=0.006, p=0.001, p=0.014, and p=0.037; respectively) were the factors related to OS, whereas the multivariate analysis determined only the age, stage, PNI, LVI, recurrence, and CA19-9 as statistically significant factors for OS (p=0.002, p=0.004, p=0.003, p=0.046, p<0.001, and p=0.002) (Table 4).

Discussion

This study evaluated the association of MPV and PDW with survival in early CC, where a low PDW and high MPV were determined as poor prognostic factors for RFS. Thrombocytosis has been shown nearly in 10% to 57% of patients with solid tumours [18]. Several studies have shown that high platelet levels might be indicative of decreased survival in some solid tumours. MPV demonstrates platelet activation and may predict the prognosis in patients with malignant tumours, although such relationship between MPV and OS remains controversial [19,20]. Altered MPV levels were found in lung cancer, gastric cancer, ovarian cancer, CRC, and breast cancer [19,20-25]. A study reported significantly higher levels of TPC and MPV in CRC patients than that in patients with colon adenomas [26]. Gao et al studied both preoperative PLT and MPV (COP-MPV) and have found that the preoperative COP-MPV can be used as an independent prognostic marker in patients with non-small cell lung cancer [27]. Marcin Włodarczyk et al. observed that preoperative MPV level was significantly lower in rectal cancer patients compared to healthy people, with and increased level after surgical resection. Furthermore, the authors also reported a negative correlation between MPV and tumor diameter [28]. Zhang et al evaluated the association of multiple clinical or pathological variables with OS/RFS in esophageal cancer and reported that COP-MPV had the best discriminatory ability for lymph node metastasis status [29]. In addition, other studies reported a significant correlation between high MPV and advanced disease stage, including gastric cancer, hepatocellular carcinoma, breast cancer, CC, lung cancer, and endometrial cancer [30-34]. In a study by Bart et al including patients with stage II to IV CC detected no association of MPV levels with survival. The authors reported that among patients who received best supportive therapy for metastatic CC, those with higher MPV levels had shorter survival than those with low MPV, albeit nonsignificant [35]. Furthermore, although Chang et al associated decreased MPV with shorter OS in univariate analysis, the multivariate analysis revealed no correlation between MPV and OS [36].

Li et al detected MPV cut-off level as 8.6 fL in their study including 243 patients with stage I to II and 266 patients with stage III to IV disease. The authors reported significantly improved 5-year OS in patients with MPV ≤8.6 fL than that in those with MPV >8.6 fL (83.6 vs 60.0%, p=0.035). Elevated MPV was determined as the most significant risk factor for survival, reporting that MPV values higher than 8.6 fL was associated 1.4-fold of increased mortality. The authors concluded MPV as an independent significant prognostic factor in patients with CRC [25].

Table 4. Relapse-free and overall survival rates at 12, 36, 60, and 120 months in PDW and MVP groups

Variables	*RFS*				*OS*			
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*		*Multivariate analysis*	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
Age (Years)		0.430				**0.002**		**0.002**
≥65	1.213 (0.751-1.959)				2.617 (1.437-4.768)		2.776 (1.441-5.348)	
<65	1				1		1	
Gender		0.965				0.743		
Female vs. Male	1.011 (0.632-1.616)				1.104 (0.611-1.994)			
Smoking		0.758				0.758		
Yes vs. no	0.926 (0.568-1.511)				0.908 (0.491-1.678)			
Alcohol		0.443				0.580		
Yes vs. no	1.334 (0.639-2.786)				1.301 (0.512-3.302)			
Obstruction/perforation		**0.012**				0.191		
Yes vs. no	2.016 (1.167-3.483)				1.631 (0.784-3.394)			
DM		0.620				**0.005**		
Yes vs. no	1.185 (0.606-2.314)				2.653 (1.340-5.251)			
HT		0.888				**0.020**		
Yes vs. no	0.964 (0.578-1.608)				2.023 (1.116-3.668)			
Histology		0.505				0.995		
Mucinous vs. others	1.236 (0.663-2.302)				1.003 (0.424-2.374)			
Grade		**0.003**				0.158		
III vs. I/II	2.878 (1.426-5.806)				2.103 (0.750-5.900)			
Localization		0.368				0.420		
Left vs. right	1.244 (0.773-2.002)				1.570 (0.525-4.701)			
Stage		**<0.001**		**<0.001**		**<0.001**		**0.004**
III vs. I/ II	5.681 (3.161-10.208)		3.467 (1.852-6.470)		3.329 (1.741-6.365)		2.691 (1.383-5.236)	
PNI		**<0.001**		**<0.001**		**<0.001**		**0.003**
Yes vs. no	5.794 (3.592-9.345)		3.023 (1.771-5.159)		3.380 (1.861-6.136)		2.750 (1.382-5.472)	
LVI		**<0.001**		**0.042**		**<0.001**		**0.046**
Yes vs. no	2.649 (1.652-4.247)		1.215 (1.060-3.870)		3.215 (1.760-5.870)		2.009 (1.013-3.986)	
Resection		0.154				0.481		
R0 vs. R1/2	2.780 (0.681-11.355)				2.041 (0.281-14.834)			
Recurrence						**<0.001**		**<0.001**
Yes vs. no					18.980 (9.841-36.603)		18.881 (9.302-38.095)	
Adjuvant CT		**0.001**		0.036		0.446		
No vs. yes	2.823 (1.222-6.520)		1.311 (1.105-6.112)		1.370 (0.610-3.079)			

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Variables	*RFS*				*OS*			
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*		*Multivariate analysis*	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
CEA elevation		**<0.001**		**0.031**		**0.006**		
ng/mL	1.062 (1.031-1.093)		1.033 (1.003-1.064)		1.060 (1.017-1.106)			
CA19-9 elevation		**0.005**		**0.007**		**0.001**		**0.002**
U/mL	1.016 (1.005-1.028)		1.019 (1.005-1.032)		1.026 (1.014-1.038)		1.019 (1.007-1.031)	
Cr elevation		0.245				0.998		
mg/dL	0.575 (0.226-1.461)				1.000 (0.366-2.732)			
AST		0.589				0.546		
U/L	0.966 (0.983-1.010)				0.928 (0.887-1.021)			
ALT		0.665				0.648		
U/L	0.998 (0.989-1.007)				0.962 (0.934-1.121)			
ALP		0.656				0.317		
U/L	0.999 (0.995-1.003)				0.997 (0.990-1.003)			
GGT		0.730				0.276		
U/L	1.001 (0.996-1.006)				0.993 (0.981-1.006)			
Albumin		0.516				0.115		
g/dL	1.292 (0.596-2.801)				0.481 (0.194-1.195)			
LDH		0.282				0.265		
U/L	0.998 (0.995-1.001)				0.996 (0.992-1.001)			
WBC		0.768				0.498		
10.5 (10^3/Ul)	0.984 (0.884-1.096)				1.044 (0.922-1.182)			
HCT		0.994				0.240		
%	1.000 (0.946-1.057)				0.960 (0.896-1.028)			
HB		0.890				0.174		
g/Dl	1.010 (0.873-1.169)				0.881 (0.733-1.058)			
MCV		0.296				0.395		
Fl	0.989 (0.968-1.010)				1.017 (0.978-1.058)			
TPC		0.247				0.794		
10^3/Ul	0.999 (0.997-1.001)				1.000 (0.998-1.002)			
RDW		0.932				0.689		
%	0.997 (0.934-1.065)				0.982 (0.900-1.072)			
MPV		**<0.001**		**0.002**		**0.014**		
Fl	1.568 (1.238-1.740)		1.184 (1.002-1.422)		1.333 (1.060-1.677)			

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Variables	*RFS*				*OS*			
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*		*Multivariate analysis*	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
PDW		**<0.001**		**0.017**		**0.037**		
%	0.95 (0.925-0.990)		0.956 (0.922-0.958)		0.976 (0.947-0.999)			
TNC		0.639				0.520		
10^3/Ul	0.847 (0.847-1.108)				1.050 (0.905-1.217)			
TLC		0.863				0.727		
10^3/Ul	1.027 (0.756-1.322)				1.073 (0.723-1.523)			
TMC		**0.034**				0.103		
10^3/Ul	2.533 (1.073-5.971)				2.547 (0.828-7.839)			

AC: adenocarcinoma; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryogenic antigen; DM: Diabetes mellitus; Cr: Creatinine; Hb: hemoglobin; R0: tumor negative surgical margin; R1/2: Tumor positive surgical margine; Hct: hematocrit; GGT: gamma glutamyl transferase; HT: hypertension; CT: chemotherapy; IQR: interquartile range; LDH: lactate dehydrogenase; LVI: lymphovascular invasion; MCV: mean corpuscular volume; MPV: mean platelet volume; OS: overall survival; PDW: platelet distribution width; PNI: perineural invasion; RDW: red blood cell distribution width; RFS: relapse-free survival; TLC: total lymphocyte count; TMC: total monocyte count; TNC: total neutrophil count; TPC: total platelet count; WBC: white blood cells.
Bold numbers denote statistical significance.

In our study, we detected MPV cut-off value for RFS as 8.5 fL. While stage I or II patients showed no difference of RFS or OS in terms of MPV groups, those in MPV >8.5 fL group had significantly shorter RFS and OS among patients with stage III disease. Increased MPV was an independent poor prognostic factor for RFS in the multivariate analysis.

Zhang et al showed that PDW was correlated with survival in patients with gastric cancer and that PDW was an independent risk factor for prognosis [11]. Zhu et al reported PDW levels in CRC patients to be significantly higher than that in the healthy control group and lower than that in patients with colon adenoma [26]. Song et al determined cut-off value of PDW as 17.25% for RFS and 17.35% for OS in their study including 206 patients with early CRC. The authors reported preoperatively increased PDW as an independent risk factor for RFS and OS in patiens with metastatic CRC [13]. We found the PDW cut-off value for RFS as 16%. While stage I or II patients did not show any difference between PDW strata with respect to RFS or OS, patients with stage III disease had improved RFS provided that their PDW were higher than 16%. Those with PDW ≤16% had median RFS of 71 months whereas median RFS was not reached in those with high PDW. Decreased PDW was determined as an independent poor prognostic factor for RFS in the multivariate analysis.

Our study has several limitations. Unlike previous studies, we did not include patients at metastatic stage or those with rectal tumors [25,35,36]. The median follow-up period was longer than that in comparable studies [13,25,35,36]. A longer follow-up period may lead to the fact that some fatal events may occur due to non-oncological reasons. This may partly explain that MPV and PDW could not be determined as independent risk factors for OS. Another limitation is that our study has a single-center and retrospective fashion. In addition, our study did not address the mechanism of the potential effect of the MPV or PDW on prognosis of the CC patients. Since the design of our study did not allow collection of patient data on RAS, RAF and microsatellite status, we do not know whether groups differ or not in such manner, or test how these potentially confound the study findings.

In conclusion, our study suggests that elevated MPV and decreased PDW appear as unfavorable prognostic factors in early CC, especially in stage III patients. Considering the wide availability and accessibility of these indices, it is reasonable to designate further larger prospective studies to clarify and verify their potential roles in early CC.

Informed consent statement

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Authors' contributions

Concept: AS, SC, SS, AbS; Design: AS, OD, CD, AbS; Supervision: NSS, AS, OD, FK; Resources: NSS, NY, CG, SA, FK; Materials: AS, NY, OD, AbS; Data Collection and/or Processing: AS, SS, NY, OD; Analysis and/or Interpretation: SC, AS, SS; CG; Literature Search: CD, CG, NSS, SA; Writing Manuscript: AS, NSS, FK, SS, SA; Critical Review: SC, CD, SS, FK; Other: SA, CG, NY

Conflict of interests

The authors declare no conflict of interests.

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