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Preoperative Platelet to Lymphocyte Ratio Predicts Early Postoperative Relapses in Patients with Stage II Colon Cancer

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Abstract

Background: Its predictive utility in patients with stage II colon cancer undergoing curative resection is yet to be fully evaluated. The purpose of this study was to evaluate its utility as a predictive maker of preoperative PLR on postoperative relapse in patients with stage II colon cancer.

Methods: A total 154 patients with stage II colon cancer who had undergone curative resection between 2007 to 2016 were eligible for this study. The present study retrospectively analyzed the data of these patients from a single hospital. Receiver Operator Characteristic (ROC) curve was applied to determine the most significant cutoff vale of PLR. Kaplan-Meier curve and Cox proportional models were used to compare high and low PLR groups and to identify the risk factor for relapse.

Results: The median PLR was significantly higher in patients who had developed tumor recurrence than in those who did not (p=0.04). Using receiver-operator characteristics curve analysis, the optimal cutoff value of PLR for the discrimination between patients who had relapse and those who did not was 198. Tumor relapses occurred significantly more frequent in patients with high PLR than compared in those with low PLR (p=0.001). Patients with low PLR were significantly better RFS than those with high PLR (95% CI 74.9-107.5, p<0.001). High PLR was an independent risk factor for RFS in multivariate analysis (HR=4.32, 95% CI=1.58-11.79, p=0.004).

Conclusion: In this study, PLR was suggested as a useful predictive marker for postoperative relapse in patients with stage II colon cancer.

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Introduction

Surgical resection with curative intent is the standard treatment for patients with localized colorectal cancer. About 20% of patients with stage II colon cancer defined by negative lymph Nodemetastasis (N0) develop tumor relapse, although the presence of lymph node metastasis is the most reliable risk factor for a poor prognosis [1]. Current international guidelines propose that adjuvant chemotherapy be considered for patients with high-risk stage II colon cancer, because postoperative relapses may result from cancer cells remaining somewhere in the patient's body after surgical resection [2,3]. In contrast, only 36% of high-risk patients with stage II colon cancer received adjuvant chemotherapy, because a significant survival benefit has not been demonstrated in such patients [4].

Previous studies have shown that the interactions between tumor and host-derived microenvironments, including inflammation, coagulation state, or immune response, contribute to the development and progression of cancer [5,6]. Recently, to predict the survival of patients with colorectal cancer, blood-based inflammatory parameters such as the Neutrophil to Lymphocyte Ratio (NLR), the Platelet to Lymphocyte Ratio (PLR), the Lymphocyte to Monocyte Ratio (LMR), C-reactive protein, and the modified Glasgow prognostic score, have been proposed as inexpensive and widely available biomarkers that are routinely measured in daily clinical practice [7-11]. Among these inflammatory markers, platelets have been shown to play an important role in several processes, such as carcinogenesis, angiogenesis, thrombosis, and metastasis in tumor growth [12,13]. This study aimed to investigate the clinical impact of the PLR on postoperative relapse in patients with stage II colon cancer after curative resection.

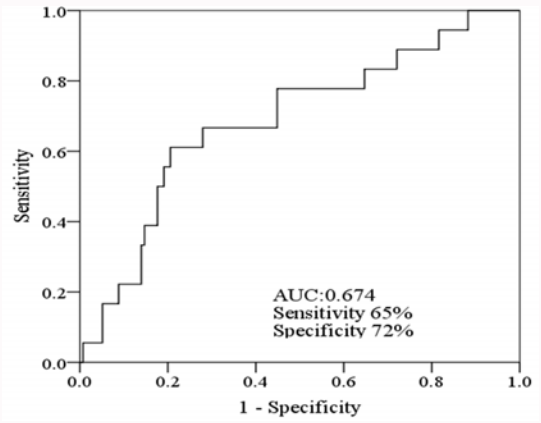

Figure 1: The receiver operating characteristics curve for relapse free survival.

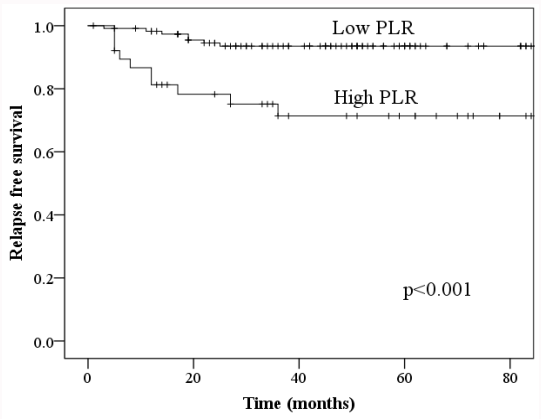

Figure 2: Kaplan-Meier curves for relapse-free survival by platelet-to-lymphocyte ratio.

Material and Methods

Patients

Between April 2007 and March 2016, the medical records of 154 patients with stage II colon adenocarcinoma at Saitama Medical Center, Dokkyo Medical University were retrospectively reviewed. Thirty-six patients who had received adjuvant chemotherapy and 3 patients who had received neoadjuvant chemotherapy were excluded. Nine patients with synchronous or metachronous, multiple advanced cancers, 1 patient with ulcerative colitis, 1 patient with liver cirrhosis, and 1 patient with malignant lymphoma were also excluded. The other exclusion criterion was that the medical records did not include the complete blood cell count, positive surgical resection margin, or history of familial CRC. This study was approved by the Ethics Committee of Saitama Medical Center, Dokkyo Medical University No.1809.

Surgical procedures and follow-up

All patients underwent curative resection including the primary tumor and enbloc dissection of regional lymph nodes up to the root of the main feeding artery (total mesocolic excision). The pathological findings were recorded by pathologists of Saitama Medical Center, Dokkyo Medical University. Cancer staging was according to the American Joint Committee on Cancer (AJCC) staging manual [14]. Postoperative surveillance including medical examinations and laboratory tests was performed every 3 months. Computed Tomography (CT) of the chest, abdomen, and pelvis was performed every 6 months. Colonoscopy for luminal surveillance was performed within 1 year after surgery and annually thereafter until no abnormality was recorded. If no abnormality was detected on surveillance colonoscopy, the subsequent colonoscopy was performed within 3 years.

Assessment of the PLR and statistical analysis

In this study, the primary end point was Relapse-Free Survival (RFS) calculated from the date of surgery to the date of the first observation of tumor relapse. The correlations between the PLR and clinicopathological characteristics were also explored. Peripheral blood obtained within 3 weeks prior to the surgery was used. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The median PLR value of each group with or without relapse was analyzed by the Mann-Whitney U test. The optimal cut-off value of the PLR for relapse was calculated using receiver operator characteristic (ROC) curve analysis. Furthermore, after patients were divided into a high-PLR group and a low-PLR group

Table 1: The baseline clinicopathological characteristics.

Characteristics	Number (%)		Number (%)
Gender		**Differentiation**	
Male	88 (57%)	Well, mod, pap	142 (92%)
Female	66 (43%)	Muc, por	12 (8%)
Age (yr)		Mucinous component	
≤ 72	84 (55%)	Absent	126 (82%)
> 72	70 (45%)	Present	28 (18%)
Preoperative serum CEA value		pT category	
≤ 5	105 (68%)	pT3	139 (90%)
> 5	49 (32%)	pT4a	11 (7%)
Preoperative serum CA19-9 value		pT4b	4 (3%)
≤ 37	133 (86%)	Lymph node yield	
< 37	21 (14%)	≥12	107 (69%)
Tumor location		<12	47 (31%)
Right	87 (56%)	Lymphatic invasion	
Left	67 (44%)	Absent	102 (66%)
Tumor size (cm)		Present	52 (34%)
≤ 5	91 (59%)	Vessel invasion	
> 5	63 (41%)	Absent	62 (40%)
Anemia		Present	92 (60%)
Absence	84 (55%)	Postoperative relapse	18 (12%)
Presence	70 (45%)	Lung	4
Glucose tolerance		Liver	6
Normal	114 (74%)	Peritoneum	3
Abnormality	40 (26%)	Local	2
Obstruction/perforation		Paraaortic lymph node	3
Absence	146 (95%)	PLR	
Presence	8 (5%)	≤ 198	39
Operation		> 198	115
Laparotomy	112 (73%)		
Laparoscopic surgery	42 (27%)		

Table 2: The correlation between clinicopathological characteristics and tumor relapse.

	Relapse		
	Presence	**Absence**	**p value**
Gender, n (%)			
Female	7 (4.5%)	59 (38%)	0.8
Male	11 (7.1%)	77 (50%)	
Age, n (%)			
≤ 72 yr	8 (5.2%)	76 (49%)	0.45
> 72 yr	10 (6.5%)	60 (39%)	
Serum CEA level, n (%)			
≤ 5	9 (5.8%)	96 (62%)	0.21
> 5	9 (5.8%)	40 (26%)	
Serum CA19-9 level, n (%)			
≤ 37	15 (9.7%)	118 (77%)	0.72
> 37	3 (1.9%)	18 (12%)	
Tumor location, n (%)			
Right	7 (4.5%)	80 (52%)	0.13
Left	11 (7.1%)	56 (36%)	
Tumor size (cm), n (%)			
≤ 5	8 (5.2%)	83 (54%)	0.21
> 5	10 (6.5%)	53 (34%)	
Anemia, n (%)			
Absence	8 (5.2%)	76 (49%)	0.45
Presence	10 (6.5%)	60 (39%)	
Glucose tolerance, n (%)			
Normal	15 (9.7%)	99 (64%)	0.41
Abnormality	3 (1.9%)	37 (24%)	
Obstruction / perforation, n (%)			
Absence	17 (11%)	129 (84%)	1
Presence	1 (1%)	7 (4.5%)	
Operation, n (%)			
Laparotomy	12 (7.8%)	100 (65%)	0.66
Laparoscopic surgery	6 (3.8%)	36 (23%)	
Differentiation, n (%)			
Well, moderately, pap	17 (11%)	125 (81%)	1
Muc, por	1 (1%)	11 (7.1%)	
Mucus component, n (%)			
Presence	4 (2.6%)	24 (16%)	0.74
Absence	14 (9%)	112 (75%)	
Tumor depth, n (%)			
pT3	15 (9.7%)	124 (81%)	0.39
pT4	3 (1.9%)	12 (7.8%)	
Lymph node yield, n (%)			
≥12	13 (8.4%)	94 (61%)	1
<12	5 (3.2%)	42 (27%)	
Lymphatic invasion, n (%)			
Absence	11 (7.1%)	91 (59%)	0.61
Presence	7 (4.5%)	45 (29%)	
Vessel invasion, n (%)			
Absence	4 (2.6%)	58 (38%)	0.13
Presence	14 (9.1%)	78 (51%)	
Serum PLR, n (%)			
≤ 198	7 (4.5%)	108 (70%)	0.001
> 198	11 (7.1%)	28 (18%)	

Table 3: Univariate analysis on RFS with different cutoff values.

	Number	**HR**	**95% CI**	**p value**
≤ 50	2	1		
50 <	152	20.44	0.00-1.484	0.77
≤100	30	1		
100 <	124	1.902	0.435-8.319	0.39
≤150	81	1		
150 <	73	2.278	0.842-6.162	0.11
≤ 200	116	1		
200 <	38	5.08	1.932-13.358	0.001
≤ 250	137	1		
250 <	17	1.931	0.554-6.726	0.3
≤ 300	141	1		
300 <	13	2.695	0.774-9.391	0.12

by the cut-off value, differences in clinicopathological characteristics between the two groups were examined by the χ^2 test or Fisher's exact test. The RFS curves were compared using the Kaplan-Meier method, and differences were evaluated by the log-rank test. Uni- and multivariate analyses to identify significant factors for RFS were performed using Cox proportional hazard regression models. All analyses were performed using the SPSS statistical software package, version 24 (IBM Japan Ltd., Tokyo, Japan). A 2-sided P value of <0.05 was considered significant.

Results

The patients' median age at the time of surgical resection was 72 years (range 29 - 89 years). The median follow-up period for RFS was 50 months (range 3 - 123 months). The baseline clinicopathological characteristics of the 154 patients are shown in Table 1. Eighteen (12%) of 154 patients developed tumor relapses, including lung (4 patients), liver (6 patients), peritoneal dissemination (3 patients), local recurrence (2 patients), and metastasis to the para-aortic lymph nodes (3 patients). Fifteen patients (15/154, 9.7%) died of any causes within the follow-up period, and ten of these patients (10/15, 67%) died of causes other than primary colon cancer.

The median PLR was 146 (range 32 - 1830). A significant difference in PLR was found between patients who developed relapse (median 208.6, range 85.0-483.3) and those who did not develop relapse (median 141.8, range 32.3-1830.2) (p=0.04). Using ROC analysis, the optimal cut-off value of the PLR for predicting relapse was 198. The largest area under the curve (AUC) for RFS was 0.688 (95% CI 0.555-0.821, p=0.01, Figure 1). When the cut-off was set to 198, the sensitivity and specificity for relapse were 65% and 72%, respectively. The tumor recurred in 11 (28%) of 39 patients with a high PLR and in 7 (6.1%) of 115 patients with a low PLR (p=0.001). On univariate proportional hazard analysis performed for PLR cut-off values of 50, 100, 200, 250, and 300, only the cut-off value of

200 showed a significant difference in RFS between patients with a high PLR and those with a low PLR (HR=5.08, 95% CI=1.93-13.36, p=0.001, Table 2).

Univariate and multivariate analyses to identify factors significantly related to RFS were performed using Cox proportional hazard models (Table 3). On univariate analyses, a serum CEA level higher than 5 ng/ml and a high PLR were associated with shorter RFS (HR=2.25, 95% CI=1.38-3.64, p=0.004 and HR=2.67, 95% CI=1.028-6.917, p=0.04, respectively). However, on multivariate analysis, a high PLR was the only factor significantly associated with shorter RFS (HR=4.32, 95% CI=1.58-11.79, p=0.004). Patients with PLR greater than 198 had a significantly increased risk of relapse compared to those with a lower PLR. The 4-year RFS was 88% for the entire study population. Figure 2 shows the Kaplan-Meier survival curves for RFS in patients according to the PLR value. Patients with a low PLR had a significantly longer RFS than those with a high PLR (95% CI 74.9-107.5, p<0.001, Figure 2). The 4-year RFS rates were 94% and 71% for patients with a low PLR and those with a high PLR, respectively. The relationships between the PLR and clinicopathological characteristics are shown in Table 4. Patients with a higher PLR had a higher serum CEA level, larger tumor size, lower hemoglobin value, and more frequent venous invasion than those with a lower PLR (p=0.005, p=0.03, p=0.001, and p=0.04, respectively) (Table 5). None of the other clinicopathological characteristics was associated with a high PLR.

Table 4: Uni-and multi-variate analyses to identify factors related to RFS.

	RFS					
Predictor	**Univariate analysis**			**Multivariate analysis**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender						
Female	1					
Male	1.09	0.414-2.859	0.86			
Age						
< 70 yr	1					
≥ 70 yr	1.59	0.587-4.293	0.36			
Anemia						
Absence	1					
Presence	1.48	0.569-3.827	0.42			
Glucose tolerance						
Normal	1					
Abnormality	1.6	0.460-5.566	0.46			
Serum CEA level						
< 5	1					
≥ 5	2.67	1.028-6.917	0.04	1.83	0.680-4.934	0.23
Serum CA19-9 level						
< 37.5	1					
≥ 37.5	1.38	0.396-4.801	0.61			
Tumor location						
Right	1					
Left	1.92	0.732-5.057	0.18			
Differentiation						
Well, moderately, pap	1					
por, muc	1.25	0.165-9.392	0.83			
Mucus component						
Absent	1					
Present	1.42	0.464-4.369	0.54			
Tumor size						
≤ 5	1					
> 5	1.68	0.647-4.347	0.29			
Tumor depth						
pT3	1					
pT4	2.12	0.609-7.382	0.24			
Lymphatic invasion						
Absent	1					
Present	1.13	0.417-3.051	0.81			
Vessel invasion						
Absent	1					
Present	2.38	0.775-7.295	0.13			
Lymph node yield						
12 or more	1					
Less than 12	1.04	0.368-2.948	0.94			
Obstruction/ perforation						
Absent	1					

Discussion

The aim of the present study was to explore its usefulness of PLR for the prediction of relapse in postoperative patients with stage II colon cancer. The median PLR value of patients who developed relapse was significantly higher than that of those who did not. Among clinicopathological characteristics, only high PLR showed a significant correlation with postoperative relapse. The Kaplan-Meier analysis revealed that patients with high PLR had significantly shorter RFS in comparison to those with low PLR. Multivariate analysis demonstrated that high PLR was independently predictive indicator of postoperative relapse in patients with stage II colon cancer. In addition, higher PLR was significantly associated with clinicopathological parameters suggesting malignant potential of colon cancer, such as higher serum CEA value, larger tumor size, and more frequent venous invasion [15,16]. Since previous trials have failed to show the benefit of adjuvant chemotherapy on patients with stage II colon cancer, most of them do not receive adjuvant chemotherapy [1,4,17,18]. However, the current international guidelines suggest that adjuvant chemotherapy should be considered for high-risk stage II colon cancer patients. As risk factor in stage II colon cancers, poorly differentiated histology, lymphovascular or perineural invasion, bowel obstruction, localized perforation, positive or incompetent resection margin, insufficient searched lymph node (<12 lymph nodes) are included [3,4]. Recent approaches using genetic and molecular markers including Microsatellite Instability (MSI), may provide better information for relapse or prognosis of cancers [19,20]. Sargent et al. [21] have reported that patients with MSI-H have a better prognosis, while fluorouracil-based adjuvant chemotherapy is not beneficial in patients with stage II colon cancer [21]. PLR is an inexpensive and easily available parameter compared to molecular and genetic markers. It has already been indicated that high PLR is associated with the prognosis of several solid cancers including ovarian, pancreatic, gastric, esophageal, and colorectal

Present	0.05	0.000-951.129	0.54			
Operation						
Laparotomy	1					
Laparoscopic surgery	1.42	0.526-3.849	0.49			
Serum PLR						
≤ 200	1					
> 200	2.25	1.384-3.641	0.001	4.32	1.581-11.792	0.004

cancers [8,22,25]. In the previous reports, however, there are few studies limited to stage II colon cancer. Ozawa et al. reported that in 234 patients with stage II colorectal cancer, patients with low PLR had significantly better prognosis regarding DFS and cancer specific survival than in those with high PLR [26]. They also reported that the PLR was an independent prognostic marker in multivariate analysis. Kim et al. reported that PLR was a prognostic indicator of both OS and DFS in patients with stage III and IV colorectal cancer [27]. In their study, however, PLR was not correlated with either OS or DFS in patients with stage I or II colorectal cancer. The difference in these results may be influence by differences in the selection criteria of the subject and whether the OS and DFS were calculated using each the cutoff value. Gu et al. [28] have indicated that the effect of platelets on cancer is different between rectal cancer and colon cancer [28]. In the carcinogenesis of rectal cancer, p53 mutation involves more commonly than in that of colon cancer, and the activation of platelet-derived growth factor receptor alpha pathway is accompanied by the suppression of p53 [13,29,30]. It has therefore been considered that the elevated platelet number may act as tumor suppressor rather than promotor. Therefore, we selected only patients with stage II colon cancer for investigating a homogeneous group of patients in the present study.

Chronic inflammation is strongly involved in carcinogenesis. This fact has been established by the observations in patients with inflammatory bowel disease. Recent experimental and clinical studies suggest several potential explanations for the association between the inflammatory and cancer [5]. Platelets promote cancer growth by increasing angiogenesis through the production of vascular endothelial growth factor, which can activate the invasiveness of tumor cell by enhancing the formation of tumor stroma and supporting the stable adhesion of tumor cells to the endothelium [31]. Labelle et al. proved that platelet-derived signals promote the formation of early metastatic niches through chemokines including CXCR5 and CXCR7 [32]. On the contrary, lymphocytes induce cytotoxic cell death of the host and are indispensable as antitumor agents which promote tumor cell apoptosis and suppress tumor metastasis [33,34]. Hence, the combination of these blood parameters appears the state of equilibrium between tumor-promoting and host-immune activity. Previous studies have proposed various cut-off values of PLR for OS, RFS, DFS, or time to recurrence (TTR) [8,26,27,35]. There is no agreement on the optimal cut-off value, because the selection criteria of patients in each study differ from each other. Diseases such as coronary artery diseases, kidney diseases, liver diseases, inflammatory disease and infectious diseases, antiplatelet agents, medication for hyperlipidemia, chemotherapy and radiotherapy may affect PLR [36]. Since these factors may influence the prognostic significance of PLR, we excluded patients complicated with ulcerative colitis, cirrhosis of the liver, malignant lymphoma, and patients who received neo- or adjuvant chemotherapy.

Table 5: The relationships between the PLR and clinicopathological characteristics.

	PLR		
	Low	**High**	**p value**
Gender, n (%)			
Female	48 (31%)	18 (12%)	0.46
Male	68 (44%)	20 (13%)	
Age, n (%)			
≤ 70 yr	55 (36%)	16 (10%)	0.58
> 70 yr	60 (39%)	23 (15%)	
Serum CEA value, n (%)			
≤ 5	86 (56%)	19 (12%)	0.005
> 5	29 (19%)	20 (13%)	
Serum CA19-9 value, n (%)			
≤ 37	102 (66%)	31 (20%)	0.18
> 37	13 (8%)	8 (6%)	
Tumor location			
Right	63 (41%)	24 (15%)	0.58
Left	52 (34%)	15 (10%)	
Tumor size (cm), n (%)			
≤ 5	74 (48%)	17 (11%)	0.03
> 5	41 (27%)	22 (14%)	
Anemia, n (%)			
Absence	72 (47%)	12 (7%)	0.001
Presence	43 (28%)	27 (18%)	
Glucose tolerance, n (%)			
Normal	86 (56%)	28 (18%)	0.83
Abnormality	29 (19%)	11 (7%)	
Obstruction/perforation			
Absent	110 (71%)	36 (23%)	0.42
Present	5 (3%)	3 (3%)	
Differentiation, n (%)			
Well, moderately, pap	106 (69%)	36 (23%)	1
Muc, por	9 (6%)	3 (2%)	
Mucus component, n (%)			
Absent	93 (60%)	33 (21%)	0.81
Present	22 (14%)	6 (5%)	
Tumor depth			
pT3	105 (68%)	34 (22%)	0.53
pT4	10 (6%)	5 (4%)	
Lymph node yield, n (%)			
≥12	79 (51%)	28 (19%)	0.84
<12	36 (23%)	11 (7%)	
Lymphatic invasion, n (%)			
Absent	77 (50%)	25 (16%)	0.85
Present	38 (25%)	14 (9%)	
Vessel invasion, n (%)			
Absent	52 (34%)	10 (6%)	0.04
Present	63 (41%)	29 (19%)	

Several previous studies have explored OS as an endpoint. However, recent advance in the treatment for metastatic and recurrent colorectal cancer appears to strongly affect the outcome. In the present study, the patients underwent surgical resection between 2007 and 2016. In the last ten years, triplet chemotherapy combined with molecular targeted therapy, late-line chemotherapy, and salvage or conversion surgery have prolonged survival of patients with recurrent colorectal cancer. In the present study, postoperative follow-up with an interval of 3 months has been carried out in majority of patients. We therefore selected RFS rather than OS or cancer specific survival as the endpoint of the present study. Actually, we also tried to obtain the cutoff value of OS using the same method as to obtain cutoff value for RFS, but only marginally significant result was obtained (p=0.053, data not shown). This study has several limitations such its retrospective design and small sample size. In addition, neither MSI nor MMR, which are recommended for predicting the prognosis of patients and the effect of adjuvant chemotherapy by NCCN guideline, have been not examined in the present study. On the contrast, the strength of this study is that the patients were relatively homogenous compared to those in the previous studies. In conclusion, the present study shows that preoperative high-PLR is a useful as a predictive indicator of relapse in patients with stage II colon cancer who underwent curative surgery. Although PLR is a convenient and inexpensive marker, it may reflect malignant potential of colon cancer, not evaluable from other clinicopathological findings. PLR therefore may be one of useful clinical indicator for the application of adjuvant chemotherapy for stage II colon cancer.

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