

Inflammation-based Indexes Upon Adjuvant Chemotherapy Initiation as a Predictor of Relapse After Curative Resection of Colorectal Cancer With an Oxaliplatin-based Regimen

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Abstract. *Background/Aim:* We investigated the clinical efficacy of inflammation-based indexes in predicting unfavourable relapse-free survival (RFS) in patients with stage II/III colorectal cancer (CRC) receiving oxaliplatin-based adjuvant chemotherapy. *Patients and Methods:* A retrospective analysis was performed on 45 patients who underwent curative resection for stage II/III CRC followed by oxaliplatin-based adjuvant chemotherapy after 8 weeks. Upon adjuvant chemotherapy initiation, all patients were evaluated for lymphocyte count (LC), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR), modified Glasgow Prognostic Score (mGPS) and prognostic nutritional index (PNI), after which their correlation with relapse was analysed. *Results:* Univariate analysis identified LC <1,350/mm³, NLR ≥2.03, LMR <5.15, PLR ≥209, mGPS 2, and early discontinuation of chemotherapy within two months as significant risk factors for RFS. Multivariate analysis identified LMR <5.15, PLR > 209 and mGPS 2 as significant independent risk factors for unfavourable RFS. *Conclusion:* Measurement of LMR, PLR, and mGPS upon adjuvant therapy initiation can be a useful tool for predicting recurrence after curative surgery for stage II/III CRC.

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Colorectal cancer (CRC) is the third most common cancer globally and the third highest cause of cancer-related deaths (1). While radical resection with lymphadenectomy remains the only curative treatment for CRC, postoperative adjuvant chemotherapy, including oxaliplatin-based therapy, has been recommended for improving outcomes in patients with stage III and high-risk stage II CRC.

Two standard adjuvant chemotherapy regimens for stage III colon cancer, namely FOLFOX [leucovorin (LV), 5-fluorouracil (5-FU) and oxaliplatin] and CAPOX (oxaliplatin and capecitabine), have been established through the MOSAIC study (2, 3), which compared LV5-FU2 therapy with FOLFOX4 therapy, and the XELOXA (NO16968) study (4), which compared CAPOX with bolus 5-FU/LV, respectively. In Japanese patients, a phase II trial for stage III colon cancer had been the first to report positive results in 130 patients receiving mFOLFOX6 or CAPOX, with a 3-year disease-free survival (DFS) of 82.2% (5). However, the aforementioned study identified stage IIIC disease and early discontinuation of therapy within 2 months as significant independent risk factors for worse DFS (5). Therefore, identifying effective prognostic biomarkers for the efficacy of adjuvant chemotherapy is imperative. Although some predictive markers have already been identified from clinicopathological characteristics, such as stage and histological grade (6-8), quite few reports have evaluated predictive biomarkers for relapse and survival among patients receiving oxaliplatin-based adjuvant chemotherapy after curative resection of stage II/III CRC (9).

Several reports have indicated that systemic inflammatory-based and nutritional indexes, including lymphocyte count (LC), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS), and prognostic nutritional index (PNI), can be useful prognostic predictors in patients with CRC (10-20). Majority of these reports had suggested the efficacy of these inflammatory indexes using data obtained upon diagnosis

or before surgery given that systemic inflammation could occur once the tumour cells potentially spread more widely beyond the resection range. Assuming this phenomenon to be true, we can hypothesize the presence of clear differences among inflammatory indexes regardless of whether residual tumour cells are observed after curative surgery.

Therefore, we focused on data obtained upon initiation of adjuvant therapy. The current retrospective study was conducted to evaluate whether inflammatory-based indexes can predict relapse in patients receiving almost unified adjuvant chemotherapy including oxaliplatin after curative resection of stage II/III CRC.

Patients and Methods

Patients. This retrospective study enrolled 45 consecutive patients who underwent curative resection of CRC in Saiseikai Kurihashi Hospital and underwent oxaliplatin-based adjuvant chemotherapy from 2012. Patients who received this adjuvant therapy were pathologically diagnosed as stage III or high-risk stage II (21).

Adjuvant chemotherapy. Adjuvant chemotherapy was initiated within 8 weeks after curative resection for CRC. Patients then received oxaliplatin-based chemotherapy including mFOLFOX6 or CAPOX over a 6-month period. The mFOLFOX6 regimen involved an intravenous infusion of 85 mg/m² of oxaliplatin and a bolus infusion of 25 mg/m² of leucovolin and 500 mg/m² of 5-FU following 2,400 mg/m² of 5-FU infusion within 46 h. This schedule was continued every 2 weeks. CAPOX involved an intravenous infusion of 130 mg/m² of oxaliplatin and 1,000 mg/m² of capecitabine administered orally twice a day consecutively for 14 days. This schedule was continued every 3 weeks.

Immuno-inflammatory indexes. Upon adjuvant chemotherapy initiation, all patients underwent haematologic and chemical examination to determine the LC, neutrophil count, monocyte count, platelet count, serum albumin (Alb), and serum C reactive protein (CRP). Thereafter, the LC, NLR, LMR, PLR, mGPS, and PNI were calculated. The mGPS was estimated using serum CRP and albumin levels as previously described (22). PNI was calculated using the following formula:

$$\text{PNI} = 10 \times \text{serum albumin level} + 5 \times \text{LC} \quad (23).$$

Follow-up. The enrolled patients were followed up after completing the scheduled treatment or until disease relapse or death. All patients were required to undergo computed tomography of the chest, abdomen, and pelvis every 6 months for surveillance.

Statistical analyses. Quantitative variables were compared *via* Student's *t*-test, whereas qualitative variables were compared using the chi square test. Cut-off values for each inflammation-based factor associated with disease relapse were determined using receiver operating characteristic (ROC) curve analysis. These factors were then divided into two categories. RFS determined using inflammation-based factors was calculated using Kaplan–Meier's method. Significant differences were identified using the log-rank test. Risk factors for RFS were assessed *via* univariate and multivariate analyses with COX

Table I. Patient background.

Age, years	Median (range)	67 (45-79)
Gender	Male/Female	30/15
Location	Colon/rectum	Oct-35
Stage*	II/IIIa/IIIb	5/20/20
CEA ng/ml	Median (range)	4.5 (0.7-194.7)
CA19-9 U/ml	Median (range)	15.4 (0.1-1,319.7)
LC, /mm ³	Median (range)	1596 (658-4,140)
NLR	Median (range)	1.95 (0.97-7.87)
LMR	Median (range)	5.01 (1.93-11.14)
PLR	Median (range)	162.7 (57.9-470.9)
mGPS	0/1/2	31/7/7
PNI	Median (range)	43.4 (12.0-52.3)
Regimen	CAPOX/FOLFOX	14/31
Discontinuation**	Early/no	9/36

*According to Japanese classification of colorectal carcinoma;

**Discontinuation of adjuvant chemotherapy within 2 months. LC: Lymphocyte count; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; PLR: platelet/lymphocyte ratio; mGPS: modified Glasgow Prognostic Score; PNI: prognostic nutritional index.

proportional regression model. Statistical analyses were performed using JMP Pro version 13 (SAS Institute Inc., Cary, NC, USA), with *p*<0.05 indicating a statistical significance.

Ethical approval. Our study protocol was approved by the Review Board of Saitamaken Saiseikai Kurihashi Hospital (Approved No. 79-4).

Results

Patient characteristics. The present study enrolled 45 patients who underwent adjuvant chemotherapy with oxaliplatin-based regimen after curative surgery between January 2012 and October 2016. All 45 patients were determined to be eligible, including 31 patients receiving mFOLFOX6 and 15 patients receiving CAPOX. The median follow-up period for survival analyses was 48 months (range=7-85 months) or until relapse for RFS. The included patients had a median age of 67 years, among whom 30 were males and 15 were females. Moreover, 35 and 10 patients had a primary tumour located at the colon and rectum, respectively. Disease stage evaluation according to the Japanese Classification revealed a pathological diagnosis of stage II in five patients, stage IIIa in 20 patients and stage IIIb in 20 patients (24). Preoperative serum CEA and CA19-9 levels, as well as inflammatory indexes upon adjuvant therapy initiation, are summarised in Table I. Nine patients discontinued treatment within 2 months due to toxicity or patient's will.

Inflammation-related indexes according to relapse. Relapse was observed in nine patients during the follow-up period. Differences in inflammation-related indexes according to recurrence are detailed in Figure 1. Notably, significant

differences in LC ($p=0.0300$), NLR ($p=0.0370$), PLR ($p=0.0486$), and mGPS ($p=0.0216$) were observed.

Cut-off values of inflammatory indexes for recurrence. The cut-off values for recurrence were determined using ROC curve analysis. Notably, a LC with the cut-off value of $1,350/\text{mm}^3$ was determined to have an area under the curve (AUC) of 0.74. Likewise, a cut-off NLR, LMR, PLR, and PNI value of 2.03, 5.15, 209, and 44.8 had an AUC of 0.73, 0.69, 0.72, and 0.63, respectively. mGPS was categorised as 0,1 or 2.

Univariate and multivariate analyses for RFS. The current study observed a 3-year RFS of 79.6%. The RFS curves according to inflammation-related indexes are presented in Figure 2. Accordingly, univariate regression analysis identified LC $<1,350/\text{mm}^3$ [hazard ratio (HR)=48.6; 95% confidence interval (95%CI)=1.56-28.18; $p=0.0090$], NLR ≥ 2.03 (HR=4.97; 95%CI=1.20-33.34; $p=0.0260$), LMR <5.15 (HR=7.89; 95%CI=1.45-146.28; $p=0.0136$), PLR ≥ 209 (HR=6.69; 95%CI=1.76-27.20; $p=0.0064$), mGPS 2 (HR=5.96; 95%CI=1.47-22.58; $p=0.0147$), and early discontinuation (HR=4.60; 95%CI=1.13-17.49; $p=0.0342$) as significant risk factors for RFS. Meanwhile, multivariate analysis identified LMR <5.15 (HR=44.1; 95% CI=2.33-3475.46; $p=0.0077$), PLR >209 (HR=10.48; 95%CI=1.26-270.86; $p=0.0278$), and mGPS 2 (HR=40.80; 95%CI=3.39-1672.58; $p=0.0022$) as significant independent risk factors for unfavourable RFS (Table II).

Discussion

The current study analysed whether several factors upon adjuvant chemotherapy initiation after radical resection could be predictive of disease relapse given that the cancer cells in most patients who develop relapse after radical resection have already potentially spread beyond the radical resection area at the time of surgery. Therefore, once the inflammatory reaction due to surgical stress subsides, some difference should be observed between cases whose cancer cells had been completely removed and those with potentially remaining cancer cells.

Given that cancer cells are generally recognised as foreign to the host, some type of inflammatory response should be induced (25-27). The current study hypothesized that inflammation-related indexes should differ depending on the presence or absence of cancer cells as described above. Moreover, only patients who received an oxaliplatin-based regimen, which is the most widely recommended adjuvant chemotherapy for CRC, were enrolled herein to control for the effects of treatment on residual cancer cells. A comparison of the inflammatory markers between the nine cases with residual cancer cells after surgery and other cases showed significant differences in some markers, including

LC, NLR, PLR, and mGPS. Thereafter, cut-off values for the inflammatory markers were calculated and examined to determine whether they would be predictive factors for RFS.

Although univariate analysis showed that some markers of inflammation and early discontinuation of adjuvant chemotherapy were risk factors for recurrence, factors including LMR <5.15 , PLR ≥ 209 , and mGPS 2 were identified as independent risk factors for poor RFS following multivariate analysis.

Yang *et al.* reported that PLR before receiving adjuvant chemoradiotherapy was an independent prognostic factor for overall survival (OS) after analysing 220 cases with stage III/IV CRC (16). In general, platelets are involved in the proliferation of tumour cells and angiogenesis, and cancer cells enhance platelet aggregation (28, 29). Owing to these interactions, PLR might be elevated in a cancer-bearing host.

A recent meta-analysis indicated that a low LMR is associated with poor survival in patients with CRC (15). Monocytes can induce tumour migration and invasion, as well as directly promote cancer cell growth (30, 31). Additionally, tumour-associated macrophages developed from circulation monocytes suppress adaptive immunity and promote angiogenesis and tumour migration (32). An increase in monocytes, in other words low LMR, might indicate the presence of metastatic tumour cells.

Several reports have demonstrated that mGPS was a useful prognostic index for CRC despite being a simple index obtained from serum CRP and Alb levels (33-35). Serum CRP levels generally increase after surgery and become negative once surgical intervention-induced inflammation subsides. In other words, CRP levels should be negative upon adjuvant chemotherapy initiation. Patients with high CRP and low Alb upon adjuvant chemotherapy initiation might have remaining metastatic tumour cells outside the resection area after surgery.

Our findings showed that LMR, PLR, and mGPS upon adjuvant therapy initiation were predictive factors for RFS, which agrees with our initial hypothesis that some inflammatory-based markers should be predictive of the presence or absence of potential metastases after radical surgery. Although this study obtained novel and significant results, several limitations are worth noting. First, given that this study was retrospective in nature, selection bias may have influenced our results. However, consecutive cases were used in this study. Second, only a limited number cases were included in this study given that it was conducted at a single institution. Data from previous clinical trials or prospective studies with a higher number of cases will be required. Finally, OS was not analysed in this report. Given that CRC can potentially be cured by R0 resection despite detection of recurrent disease and progression of chemotherapy after recurrence, a longer observation period is needed. Therefore, longer observation periods are required

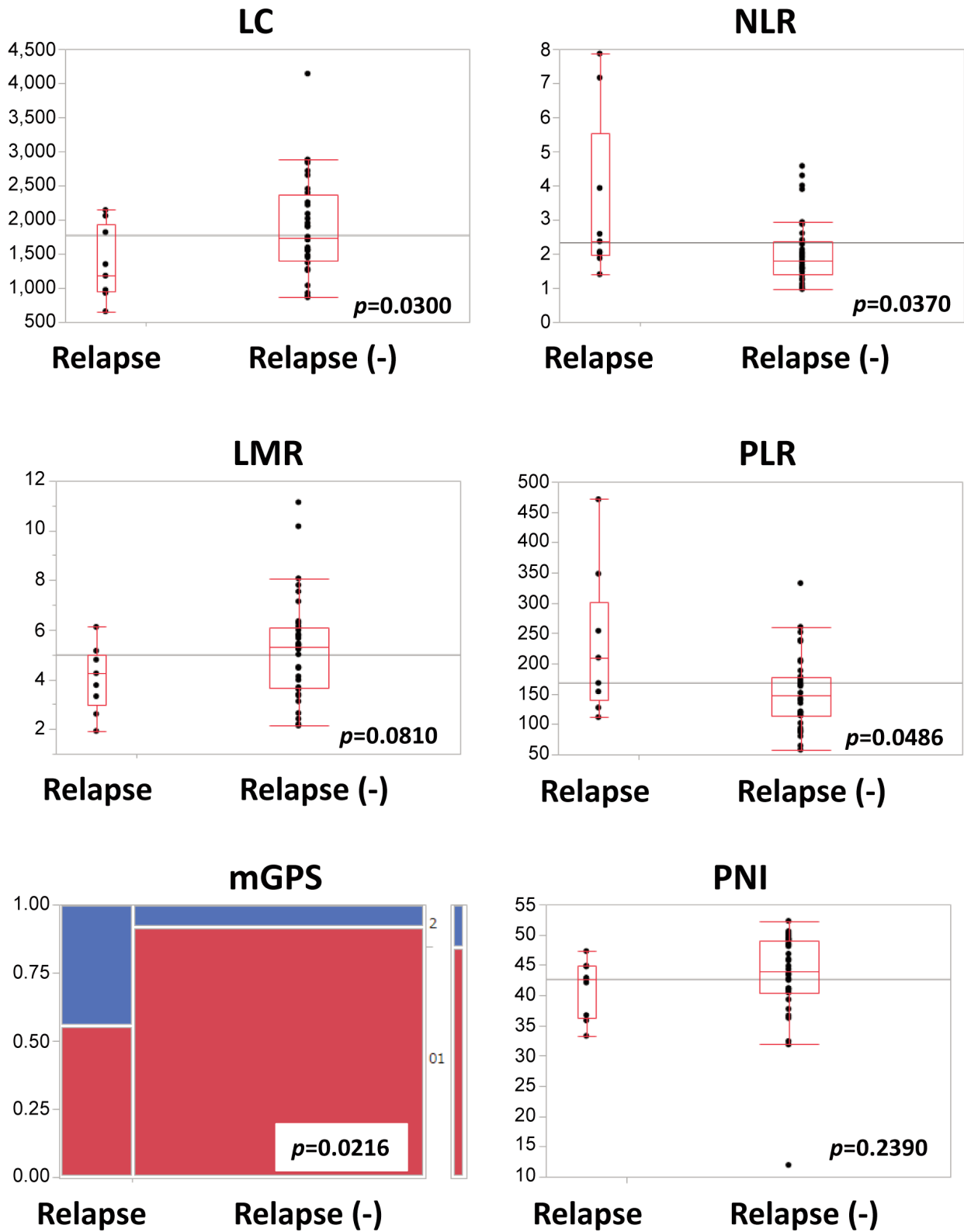


Figure 1. Inflammation-related indexes according to relapse. Significant differences were observed for LC ($p=0.0300$), NLR ($p=0.0370$), PLR ($p=0.0486$), and mGPS ($p=0.0216$). LC: Lymphocyte count; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; mGPS: modified Glasgow Prognostic Score.

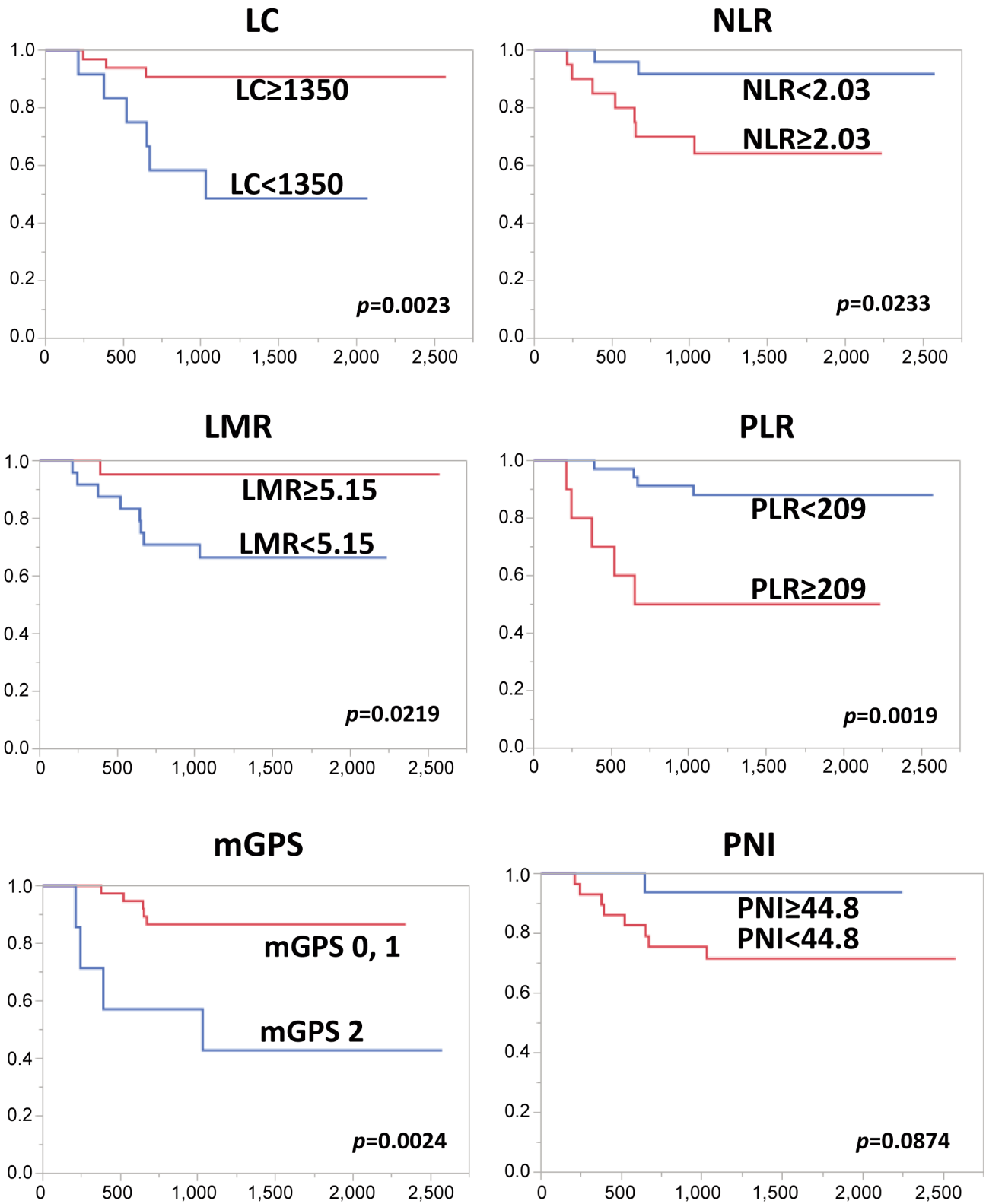


Figure 2. Relapse-free survival curves according to inflammation-related indexes. Significant differences were observed in LC ($p=0.0023$), NLR ($p=0.0233$), LMR ($p=0.0219$), PLR ($p=0.0019$), and mGPS ($p=0.0024$). LC: Lymphocyte count; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; PLR: platelet/lymphocyte ratio; mGPS: modified Glasgow Prognostic Score.

Table II. Risk factors for recurrence-free survival.

Factor	3Y RFS	Univariate			Multivariate		
		HR	95%CI	p-Value	HR	95%CI	p-Value
Stage IIIb	75	1.6	0.42-6.46	0.4839			
CEA >5 ng/ml	83	0.95	0.19-4.31	0.9454			
CA19-9 >37 U/ml	87.5	0.55	0.03-3.22	0.5739			
LC <1.350/mm ³	48.6	5.94	1.56-28.18	0.009	1.57	0.30-9.74	0.6397
NLR ≥2.03	64.2	4.97	1.20-33.34	0.026	4.03	0.23-179.95	0.5987
LMR <5.15	66.4	7.89	1.45-146.28	0.0136	44.31	2.33-3475.46	0.0077
PLR ≥209	50	6.69	1.76-27.20	0.0064	10.48	1.26-270.86	0.0278
mGPS 2	42.9	5.96	1.47-22.58	0.0147	40.8	3.39-1672.58	0.0022
PNI <44.8	71.6	4.9	0.90-90.95	0.0692			
CAPOX regimen	71.4	2.19	0.53-8.51	0.2642			
Early discontinuation	48.6	4.6	1.13-17.49	0.0342	1.67	0.23-33.60	0.6397

LC: Lymphocyte count; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; PLR: platelet/lymphocyte ratio; mGPS: modified Glasgow Prognostic Score; PNI: prognostic nutritional index; CAPOX: oxaliplatin and capecitabine.

to determine whether the identified indexes can be used as prognostic factors for OS.

In conclusion, this novel study demonstrated that LMR, PLR, and mGPS upon adjuvant therapy initiation after curative resection for stage II/III CRC were significant indicators for RFS. Larger prospective studies are warranted for the validation of the preliminary results obtained in the present study.

Conflicts of Interest

All Authors have no conflicts of interest in relation to this study.

Authors’ Contributions

Satake M and Yoshimatsu K contributed to planning this study, analyse the data and prepare the manuscript. Sagawa M helped with the statistical analyses. Yokomizo H and Shiozawa S supervised this study.

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