

Peripheral Blood Platelet–Lymphocyte Ratio Is Good Predictor of Chemosensitivity and Prognosis in Gastric Cancer Patients

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Introduction: Platelets are one factor promoting tumor development. Conversely, lymphocytes are one factor for immune protection. The peripheral blood platelets–lymphocyte ratio (PLR) is useful as an inflammation/immune indicator to predict postoperative recurrence and prognosis of a variety of malignancies. The peripheral blood neutrophil–lymphocyte ratio (NLR) has also been reported as a useful inflammation/immune indicator. However, there are few studies evaluating the relationship between these peripheral blood indicators and the effectiveness of chemotherapy. Thus, we examined these relationships in gastric cancer patients.

Patients and Methods: Between 2005 and 2018, 41 gastric cancer patients treated with preoperative DCS therapy (docetaxel, cisplatin, and S-1) therapy followed by gastrectomy were evaluated. Data for peripheral blood tests prior to the initiation of chemotherapy were used. The effectiveness of chemotherapy was determined using Response Evaluation Criteria in Solid Tumors (RECIST) and the pathological response of primary lesions (Ef grade). The relationship between the blood test results and the effectiveness of chemotherapy was evaluated.

Results: Each optimal cut-off value of peripheral inflammation/immune indicators was calculated through ROC curves. Although the pathological responder (Ef grade 2 or 3) revealed significantly better prognosis than the non-responder (Ef grade 0-1b), no relationship was found between responder according to RECIST and prognosis ($P=0.014$, $P=0.992$). In univariate analysis, a low PLR (<180 , $P=0.005$), low NLR (<2.6 , $P=0.019$), high lymphocyte (≥ 1.43 , $P=0.019$) and high PNI (≥ 40 , $P=0.032$) were identified as prognostic markers, whereas PLR was the only marker correlated with pathological response ($P=0.031$).

Conclusion: PLR obtained prior to chemotherapy might be a useful indicator for predicting chemosensitivity owing to the simplicity of its procedure.

Keywords: gastric cancer, preoperative chemotherapy, chemosensitivity, platelet-lymphocyte ratio

Introduction

Gastric cancer is a major cause of cancer-related deaths in East Asia. Multidisciplinary therapy combining chemotherapy with surgery is considered to be important for treating this disease. The safety and efficacy of preoperative chemotherapy have been reported by multiple studies in recent years.^{1–3} The JCOG0405 (Japan Clinical Oncology Group) study reported the safety of S-1 plus cisplatin treatment as preoperative chemotherapy followed by D2 gastrectomy with para-aortic lymph node dissection. The 3- and 5-year overall survival rate of

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this approach is 59% and 53%, respectively, which suggests its effectiveness.³ However, some patients who show no response to chemotherapy have fatal outcomes because of delayed surgery. For this reason, a predictive biomarker for the effectiveness of chemotherapy is required.

Extravascular platelets deposited in the cancer microenvironment have been reported as a short-term prognostic factor and are related to anticancer drug resistance.⁴ These effects are thought to be a result of microparticles from activated platelets, such as vascular endothelial growth factor (VEGF) and transforming growth factor- β (TGF- β), both of which promote tumor development. Many reports identify platelets as cancer development factors,^{5–7} however, immunostaining is required for identifying extravascular platelets. Hence, new simple biomarkers should be explored.

Peripheral blood inflammation/immuno-nutrition indicators, such as the platelets–lymphocyte ratio (PLR), neutrophil–lymphocyte ratio (NLR), and prognostic nutritional index (PNI), are widely recognized as useful prognostic predictors in various malignancies.^{8–11} A low NLR or a high peripheral lymphocyte count could be predictors for a high efficacy of preoperative chemotherapy for breast cancer patients.^{12–14} To our knowledge, this is the first report to investigate whether a peripheral inflammation/immuno-nutrition indicator could predict the efficacy of preoperative chemotherapy in gastric cancer.

Patients and Methods

Ethical Approval

Prior to the research, written informed consent was obtained from each patient. The present study was in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Institutional Review Board of Kanazawa University Graduate School of Medical Science (Study permission number 1840-1).

Patients

Forty-one patients with advanced gastric cancer between 2005 and 2018 in whom preoperative modified DCS (mDCS) therapy was administered were selected as the study subjects and were retrospectively analyzed. The eligibility criteria were as follows: all gastric cancer patients (either cStage III or cStage IV) with ≤ 3 peripheral liver metastases and para-aortic lymph node metastases.

According to the Japanese Classification of Gastric Cancer (JGC) 3rd English edition,¹⁵ para-aortic lymph node metastasis is defined as a swelling of ≥ 10 mm on a 2.5-mm slice contrast-CT scan. An absence of peritoneal dissemination was confirmed by intraperitoneal observation. Patients aged between 20 and 80 years with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) rank from 0 to 1 were included. No other preoperative chemotherapy, radiation therapy, or gastric surgery were administered to any of the patients. No patient had any signs of hemorrhage from the primary lesion. The oral intake of the patients was favorable and hematopoietic, liver, and kidney functions were all maintained. The following patients were excluded from the study: patients with cardiovascular disease, pulmonary fibrosis, hemorrhaging tendencies, poorly controlled high blood pressure, diabetes mellitus, active malignancy, central nervous system disease, history of severe drug allergy, and pregnant, or breastfeeding patients. The blood test results used were obtained within 1 week prior to the initiation of chemotherapy. When multiple results within this 1-week period were available, the latest one was used.

Treatment

mDCS therapy that originated in Kanazawa University was used as preoperative chemotherapy with the goal of reducing the adverse effects and enhancing the effectiveness of the chemotherapy.^{16–18} The content of the protocol was as follows: 35 mg/m² docetaxel as a 1-h IV drip on days 1 and 15, and 35 mg/m² cisplatin as 2-h IV drip with simultaneous maintenance of hydration on days 1 and 15. S1 was administered orally at a dosage of 80 mg/m² on days 1 through 14. One cycle lasted for 4 weeks, and only patients for whom a minimum of two cycles was administered were chosen as subjects. The surgical treatments were complete gastrectomy, D2 lymph node dissection, para-aortic lymph node dissection, and hepatectomy for R0 resection. The para-aortic lymph nodes were defined as lymph nodes 16a2 and b1 between the upper edge of the celiac artery and the lower edge of the inferior mesenteric artery.

Response Evaluation

Following two cycles of preoperative mDCS therapy, tumor regression was evaluated by a contrast-CT scan using RECIST.¹⁹ The evaluation categories were as follows: complete response (CR, complete disappearance the tumor), partial response (PR, reduction of tumor by $\geq 30\%$

or more), progressive disease (PD, enlargement of tumor by $\geq 20\%$), and stable disease (SD, reduction less than PR or enlargement less than PD). Within these RECIST criteria, CR and PR cases were considered responders.

The pathological effectiveness of chemotherapy was also judged in accordance with the categories defined in the JCGC (3rd English Edition). The five classifications range from complete response (Grade 3) to no effect (Grade 0). The subjects were rated as follows depending on the degree of degeneration or necrosis of the invasive cancer cells: Grade 1a: $\geq 2/3$ of remaining cancer cells, Grade 1b: $1/3$ to $2/3$ of remaining cancer cells, and Grade 2: $<1/3$ of remaining cancer cells. Grades 2 and 3 were considered pathological responses in this study. All specimens were evaluated by two independent pathologists.

Statistical Analyses

PLR, NLR, neutrophil-to-monocyte ratio (NMR), and lymphocyte-to-monocyte ratio (LMR) were calculated based on the peripheral blood test. PNI was calculated based on serum albumin values and peripheral blood lymphocyte count was calculated as $[PNI = (10 \times \text{albumin}) + (0.005 \times \text{TLC (total lymphocyte count)})]$. Through receiver operating characteristic (ROC) curve analysis, we obtained the optimal cut-off levels and areas under the curves (AUCs) of routine blood parameters and their ratios, as shown in Table 1. The Ef grade was applied to select the optimal cut-off points. In addition, we adopted the upper limit at our hospital as the cut-off value for CRP and tumor markers, such as CEA, CA19-9, CA125, and AFP. Fisher's test was used to determine the difference in the clinicopathological parameters and chemotherapy response. The Kaplan–Meier method and the Log-rank

test were used for survival analysis. Multivariate analysis was performed using the Cox hazard model as the prognostic parameters. $P < 0.05$ was considered statistically significant. SPSS version 23 (IBM Corp., Armonk, NY, USA) was used for the analyses.

Results

Characteristics of the Patients

Forty-one patients who received mDCS therapy as preoperative chemotherapy treatment between 2005 and 2018 were included. The characteristics of the patients are shown in Table 2. Para-aortic lymph node metastasis was

Table 2 Patient Characteristics

Characteristics		
Number of patients		41
Age: median (range)		65 (30–78)
Gender	Male	34
	Female	7
ECOG performance status	≥ 1	13
	0	28
Differentiation	Poorly	19
	Moderate-well	22
Clinical T stage	cT1	0
	cT2	4
	cT3	13
	cT4	24
Clinical N stage	cN0	2
	cN1	2
	cN2	19
	cN3	18
Clinical stage	0	0
	I	0
	II	0
	III	14
RECIST	IV	27
	CR	0
	PR	29
	SD	11
Histological evaluation criteria (Grade)	PD	1
	3	2
	2	19
	1b	3
	1a	16

Table 1 Optimal Cut-Off Values Together with AUCs

Variates	AUC	Cut-off Point
PLR	0.682	180
NLR	0.626	2.4
NMR	0.535	1.1
LMR	0.462	4.01
Platelet	0.666	$240 \times 10^9/L$
Lymphocyte	0.493	$1.43 \times 10^9/L$
Neutrophil	0.562	$4.1 \times 10^9/L$
Monocyte	0.521	$0.33 \times 10^9/L$
PNI	0.502	40
Albumin	0.464	3.6 g/dL

Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

identified in 16 patients (39%), and liver metastasis was identified in 9 patients (22%). The preoperative clinical tumor stage was stage III in 14 patients and stage IV in 27 patients.

Response Rates

Among the patients receiving preoperative mDCS treatment, 29 patients (70.1%) were identified by RECIST as clinical responders and 21 patients (51.2%) were identified as pathological responders.

Relationships Between Overall Survival and Clinicopathological Parameters

Table 3 shows the relationships between OS and each clinicopathological factors. In the univariate analysis, lower Ef grade was identified as a risk factor for OS ($P=0.014$). Furthermore, significant differences were

Table 3 Univariate/Multivariate Analyses of Factors Associated with Prognosis

Parameters (Cut-off Point)	Univariate P-value	Multivariate HR (95% CI)	P-value
Age	0.329	0.379(0.092–1.555)	0.178
Gender	0.037		
PS	0.264		
Differentiation	0.319		
TNM stage	0.75		
T stage	0.676		
N stage	0.665		
RECIST	0.992		
Histological evaluation criteria	0.014	2.672(0.812–8.794)	0.106
PLR (180)	0.005	4.778(0.984–23.205)	0.052
NLR (2.4)	0.019	0.588(0.116–2.987)	0.522
NMR (1.1)	0.661	1.360(0.328–5.639)	0.672
LMR (4.05)	0.07		
Platelet (240)	0.839		
Lymphocyte (1.43)	0.019		
Neutrophil (4.1)	0.533		
Monocyte (0.33)	0.861		
PNI (40)	0.032		
CEA (5)	0.519	3.680(0.981–13.808)	0.054
CA19-9 (37)	0.232	3.680(0.981–13.808)	0.054
CA125 (35)	0.15		
AFP (10)	0.621		
Albumin (3.6)	0.118		
CRP (1.0)	0.302		

Abbreviations: HR, hazard ratio; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

identified in the blood test findings in the high PLR group ($P=0.005$), high NLR group ($P=0.019$), low lymphocyte group ($P=0.019$) and low PNI group ($P=0.032$) all of whom exhibiting shortened OS in the univariate analysis. No significant difference was identified in the multivariate analysis. As shown in Figure 1, Kaplan–Meier curves revealed significantly better survival in lower PLR, lower NLR, high lymphocytes, and high PNI group.

Relationship Between the Efficacy of Chemotherapy and Hematological Parameters

There was no relationship between RECIST and any factor (data not shown). Table 4 shows the relationship between Ef grade and each factor. Among the 20 patients in the high PLR group, a pathological response was identified in 6 patients (30%), while 14 patients (70%) were unresponsive. Of the 21 patients in the low PLR group, a pathological response was identified in 15 patients (71%), while 6 patients (29%) were unresponsive. A statistically significant correlation with chemotherapy resistance was identified in the high PLR group ($P=0.031$). Of the 22 patients in the high NLR group, a pathological response was identified in 9 patients (41%), while 13 patients (59%) were unresponsive. Of the 19 patients in the low NLR group, a pathological response was identified in 12 patients (63%), while 7 patients (37%) were unresponsive. No statistically significant correlation with the pathological response was identified in the values of NLR ($P=0.155$) and PNI ($P=0.914$).

Discussion

S-1 is a standard anticancer drug used for the treatment of locally advanced gastric cancers in Japan.²⁰ Some studies have indicated its effectiveness as preoperative chemotherapy.^{1–3,21–23} When choosing a treatment regimen, predicting the effectiveness of the drugs is crucial.

It is thought that systemic inflammation and tumor-related micro-environments play an important role in modulating chemotherapy resistance.^{24–26} However, the related mechanism of action remains largely unknown.⁴ Although PLR, NLR, and other hematological markers including nutrition indicators have been established as effective prognostic factors for numerous types of cancers,^{8–11} the relationship between these markers and chemotherapy resistance is also unclear.

In this study, only PLR was linked to chemotherapy resistance, but not NLR and PNI.

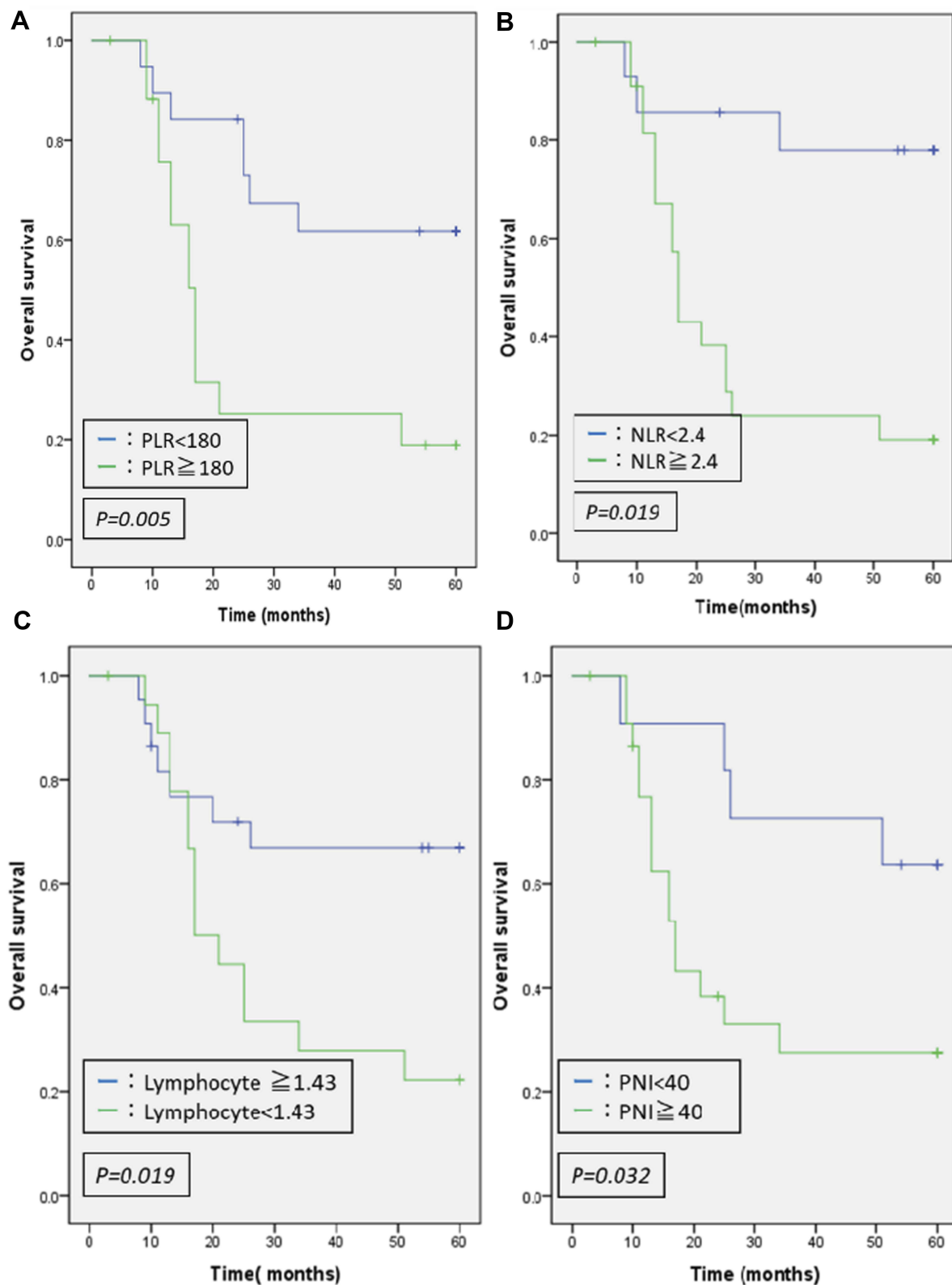


Figure 1 Overall survival curves for different inflammatory/immune-nutrition indicator. Significantly shorter survivals were shown in patients with high PLR (A), high NLR (B), low lymphocyte (C), and low PNI (D).

Table 4 Relationship Between Ef Grade[†] and Each Parameter

Parameters	Total,N	Ef Grade 0-1b(N)	Ef Grade 2-3(N)	χ^2	Univariate P-value	Multivariate HR (95% CI)	P-value
Age, years <70 ≥70	28 13	13 7	15 6	0.196	0.658		
Gender Male Female	34 7	18 2	16 5	1.38	0.24		
PS 0 I	28 13	13 7	15 6	0.196	0.658		
Differentiation Poorly differentiated Moderate-well differentiated	19 22	6 14	13 8	4.193	0.041	0.480(0.183–1.256)	0.135
PLR <180 ≥180	21 20	6 14	15 6	4.659	0.031	1.993(0.793–5.008)	0.143
NLR <2.4 ≥2.4	19 22	7 13	12 9	2.02	0.155		
NMR <1.1 ≥1.1	19 22	9 11	10 11	0.028	0.867		
LMR <4.05 ≥4.05	21 20	9 11	12 9	0.605	0.437		
Platelet <240 ≥240	18 23	6 14	12 9	3.064	0.08		
Lymphocyte <1.43 ≥1.43	19 22	9 11	10 11	0.028	0.867		
Neutrophil <4.1 ≥4.1	20 21	10 10	10 11	0.023	0.879		
Monocyte <0.33 ≥0.33	17 24	7 13	10 11	0.266	0.606		
PNI <40 40-	23 11	13 6	10 5	0.012	0.914		
CEA <5 ≥5	22 14	13 7	9 7	0.286	0.593		

(Continued)

Table 4 (Continued).

Parameters	Total,N	Ef Grade 0-1b(N)	Ef Grade 2-3(N)	χ^2	Univariate P-value	Multivariate HR (95% CI)	P-value
CA19-9 <37 ≥ 37	27 9	16 4	11 5	0.6	0.439		
CA125 <35 ≥ 35	31 4	19 1	12 3	1.905	0.167		
AFP <10 ≥ 10	28 3	15 3	13 0	2.399	0.121		
Albumin <3.6 ≥ 3.6	7 27	5 14	2 13	0.864	0.353		
CRP <1.00 ≥ 1.00	21 8	13 2	8 6	3.16	0.075		

Notes: [†]The histological evaluation criteria were classified into five categories ranging from the complete response (Grade 3) to no effect (Grade 0) in the JCGC (3rd English Edition) as Ef grade.

Abbreviations: HR, hazard ratio; PS, performance status; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

We have previously reported that a primary lesion with platelet infiltration as CD42b positive cells revealed chemo-resistance.⁴ We focused on the role of circulating platelets in this study. Circulating platelets attach and aggregate to the vascular wall via von Willebrand factor (vWF), which released from damaged endothelial cells by cisplatin-based chemotherapy.²⁷

Aggregated and activated platelets release several chemical mediators, such as TGF- β and VEGF-A.²⁸ TGF- β signaling contributes to epithelial-mesenchymal transition (EMT), which induces upregulation of metastatic ability and chemo-resistance in cancer cells.²⁹

Recent studies have revealed that Foxp3⁺CD25⁺CD4⁺ regulatory T cells (Tregs), which are physiologically engaged in maintaining immunological self-tolerance, play critical roles in the control of antitumor immune responses.³⁰ TGF- β also plays an important role in the induction and maintenance of Tregs via Foxp3 activation.³¹

Angiogenesis induced by VEGF-A reveals irregularly shaped and hyperpermeable vessels, which result in impaired oxygen and drug delivery within the tumor.³² VEGF-A can increase the recruitment of Treg and myeloid-derived suppressor cells (MDSCs), and hinder the differentiation and activation of dendritic cells.³³

A reduction in the lymphocyte count in the peripheral blood might cause a restriction in tumor-infiltrating lymphocytes (TIL), which are involved in the antitumor activity.

In cancer patients, it has been reported that a reduction in the lymphocyte count can indicate an inadequate immune response to cancer cells.³⁴ A number of reports have documented the association of a high peripheral blood lymphocytes (PBL) count and a favorable prognosis.^{35,36} In addition, an increase in TIL is reportedly associated with an improved prognosis in cancer patients.³⁷ By contrast, the level of TILs is a strong predictor of the efficacy of NAC in breast cancer,³⁸ and it is assumed that a high peripheral lymphocyte count is a useful predictor of pCR in breast cancer patients with NAC.¹⁴ A high peripheral lymphocyte count may play a crucial role not only in the systemic anticancer immunological response but also in direct effects on local tumor cells. However, the direct relationship between PBL and TIL has not been sufficiently understood.

These positive relationships between the PBL count and local immunity are justified by the cancer-immunity cycle.³⁹ PBL continually enters and exits lymph nodes, resulting in priming and activation by antigen-presenting dendritic cells (DCs). These lymphocytes can migrate and

infiltrate to the cancer microenvironments. However, it is essential that DCs can recognize neoantigens from cancer cells, which are induced by immunogenic chemotherapy.⁴⁰ Thus, the efficacy of chemotherapy depends on systemic and local immunity can activate the adaptive immune system and sensitize tumor cells to T-cell-mediated killing. Accordingly, peripheral lymphocyte counts strongly affect TIL count, resulting in reflecting chemosensitivity.

This study has some limitations. First, the efficacy of only one chemotherapy regimen (mDCS therapy) evaluated the correlation with peripheral inflammation/immune indicators. However, PLR should be considered a reliable predictor of chemosensitivity, because mDCS therapy consists of three typical agents, taxane, platinum, and fluorouracil, which are widely used for gastric cancer treatment worldwide. Second, there was no relationship between PLR and RECIST in this study. RECIST criteria is based on CT image, and according to common cut-off values of metastatic lymph node, positive prediction values as 77% and sensitivity was 62%.⁴¹ Therefore, RECIST responder is not always true responder.⁴² In gastric cancer, overall survival also correlated with Ef grade, but not RECIST.⁴³ These are why there was significant relationship between PLR and Ef grade, but not RECIST. Third, this study was conducted retrospectively on a small scale in subjects included from a single medical institution. Future multi-institutional joint research studies on a large scale are essential for corroboration of these results.

Conclusion

Our study suggested that PLR including both platelets as a negative factor and lymphocytes as a positive factor for cancer immunity is a simple and useful predictor for chemosensitivity, which can be measured at any facility.

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Disclosure

The authors report no conflicts of interest in this work.

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