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Relationship Between FDG Uptake and the Platelet/lymphocyte Ratio in Patients With Breast Invasive Ductal Cancer

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Abstract. *Background/Aim: We investigated the relationship between F18-fluorodeoxyglucose (FDG) uptake and the platelet/lymphocyte ratio (PLR), as both represent inflammation. Patients and Methods: We retrospectively analyzed the cases of 143 consecutive invasive ductal carcinoma patients who had undergone preoperative FDG-PET and surgery. We divided the patients into groups based on their maximum standardized uptake value (SUVmax) values: low (<2.5) and high (≥2.5) and based on their PLRs: low (<130) and high (≥130). We determined the relationships between the SUVmax or PLR and clinicopathological features. Results: Seventy-three patients (51.0%) had a high SUVmax in their primary tumor. There were significant associations between SUVmax and the PLR. A multivariate analysis revealed that high PLR, but not NLR, was independent factor associated with a high SUVmax. Seventy-four patients (51.7%) had a high PLR; The factors significantly associated with high PLR were large tumor size, presence of node metastasis, presence of vascular invasion, high NLR, and high SUVmax. Conclusion: In breast cancer patients, the PLR is independently associated with the SUVmax, but not with recurrent disease. In breast cancer patients with a high SUVmax and/or PLR, these values may reflect the tumor microenvironment.*

An increasing amount of evidence indicates that the presence of a systemic inflammatory response is associated with poor survival in multiple types of cancer (1-8). Cancer progression and prognosis are affected by the host's inflammatory response in the tumor microenvironment (1, 2). Accordingly, inflammation-based prognostic indicators such as the C-reactive protein (CRP) level, the neutrophil/lymphocyte ratio (NLR), and the platelet/lymphocyte ratio (PLR) have been investigated in breast cancer (2, 4, 5, 8-15). It is of interest that the presence of a systemic inflammatory response, as evidenced by an elevated PLR, was found to be a prognostic factor in breast cancer (2, 14, 15).

In recent years, the clinical applications of positron emission tomography (PET) have grown explosively. PET using F18-fluorodeoxyglucose (FDG) is a noninvasive whole-body imaging technique used to evaluate various types of malignancies (including breast cancer) for tumor staging and restaging, detecting recurrence, and monitoring treatment responses (16-24). FDG-PET measures the glucose metabolism, which reflects the biological aggressiveness of cancers (24-29). Several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer (24-29).

The uptake of FDG is influenced by many factors (including inflammation), and we reported that FDG uptake was associated with the NLR (8). However, to the best of our knowledge, no published study has assessed the association between the FDG uptake and the PLR in breast cancer patients, though both represent inflammation. In this study, we investigated the relationship between FDG uptake and the PLR, an indicator of systemic inflammation, in patients with breast cancer at baseline.

Patients and Methods

Patients. We retrospectively analyzed the cases of 143 consecutive patients with primary breast cancer who had undergone FDG-PET preoperatively at Gunma University between January 2010 and October 2015. All patients had already undergone radical breast surgery. Patients with synchronous bilateral breast cancer or clinical signs of infection or other inflammatory conditions preoperatively, including pneumonia or articular rheumatism, were excluded from the study. Patients with incomplete clinical information and male patients were excluded.

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All of the patients underwent FDG-PET/computed tomography (CT) as part of the routine standard of care without deviations from the main protocol. The maximum standardized uptake value (SUVmax) of the patient's primary tumors was calculated in a routine clinical fashion. Written consent was obtained from all patients for the use of their records and imaging in future studies, and this was approved by our Clinical Ethics Committee.

The details extracted from the database were the patient' age, tumor's histological type, size of the invasive primary tumor, size of ductal spread, presence/absence of lymphatic or vascular invasion, nuclear grade, estrogen receptor (ER) expression status and progesterone receptor (PgR) expression status, human epidermal growth factor receptor 2 (HER2) score of the primary tumor, axillary lymph node status, serum CRP level, values of the serum tumor marker carcinoembryonic antigen (CEA), hemogram parameters (neutrophils and lymphocyte), SUVmax of the primary tumor, and visibility of detected lesion by FDG-PET. The ER and PgR statuses were assessed by Allred score, with an Allred score of ≥3 indicating ER and PgR positivity (30).

We defined the PLR as the platelet count divided by the absolute lymphocyte count. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The relationships between the SUVmax and clinicopathological features, including the PLR, were investigated.

The median SUVmax of all 143 patients was 2.5 (range=0-10.5). We divided the patients into two groups based on their SUVmax values: low (<2.5) and high (≥2.5). The median PLR of the patients was 130 (range=67.5-387.8): we divided the patients into two groups based on their PLRs: low (<130) and high (≥130).

Statistical analyses. The breast cancer cases were divided on the basis of both their FDG uptake and the PLR in their primary tumors. We conducted a univariate statistical analysis using Fisher's exact test or the c^2 test with Yates' correction. For the comparisons of pairs of groups, we used Student's *t*-test. Differences were considered significant when $p<0.05$. To test the independence of the factors related to a high SUVmax value, we entered the variables with a likelihood of $p<0.05$ into a multivariate logistic regression model.

Results

The median SUVmax of the 143 patients was 2.5 (range=0-10.5). Seventy-three patients (51.0%) had a high SUVmax in their primary tumor. Table I summarizes the characteristics of the patients in the two SUVmax groups and presents the results of the univariate analysis conducted to determine the relationships between the primary tumors' SUVmax values and the clinicopathologic variables. The variables that were significantly associated with a high SUVmax in the primary tumor were as follows: large tumor size ($p<0.001$), high nuclear grade ($p<0.001$), the presence of lymphovascular invasion ($p<0.001$), high CRP level ($p=0.046$), high NLR ($p<0.001$) and high PLR ($p<0.001$). There was a significant association between the SUVmax and the PLR (r=0.376, $p<0.001$). The multivariate analysis revealed that only large tumor size ($p<0.001$), high nuclear grade ($p<0.001$) and high PLR ($p=0.004$) were significantly associated with a high SUVmax.

The median PLR of the 143 patients was 130 (range=67.5-387.8). Seventy-four patients (51.7%) had a high PLR, and the other 69 patients (48.3%) had a low PLR. The 143 cases with breast cancer were divided into two groups based on PLR in the primary tumor. Table II shows the patients' characteristics and summarizes the results of the univariate analysis conducted to determine the relationships between PLR and various clinicopathologic variables. The present univariate analysis revealed that large tumor size ($p=0.019$), the presence of node metastasis ($p=0.015$), the presence of vascular invasion ($p=0.045$), high NLR ($p<0.001$) and high SUVmax ($p<0.001$) were significantly associated with a high PLR.

In our previous study of patients with breast cancer, the period of relapse-free survival (RFS) shown by Kaplan-Meier curves was significantly shorter for patients with a high SUVmax (8). The overall median follow-up period was 48.9 months (range=9.6-94.7 months). Among the 70 cases with low SUVmax, there was no recurrent disease, whereas six of the 73 cases with a high SUVmax had disease recurrence (8). However, our present analyses revealed that the PLR was not associated with recurrent disease in patients with breast cancer.

Discussion

Inflammation is a significant problem in cancer patients because of a variety of mechanisms involving the tumor and the host response to the tumor. Many recent studies have focused on the correlation between inflammation and solid malignancies, and they revealed that tumor initiation, progression, and metastasis are all affected by the host systemic inflammatory response as well as the tumor microenvironment (15). The PLR is considered as important as the CRP level and the NLR in assessment of the inflammatory status, and the PLR and NLR were reported to be prognostic factors in breast cancer (2, 14, 15). FDG-PET shows inflammation and provides biological information about a tumor's growth potential. Several studies have reported that high FDG uptake is predictive of both poor prognosis and aggressive features in patients with breast cancer (24-29).

The key observations of our present study are as follows: in patients with operable breast cancer, 1) among various clinicopathological characteristics, a high SUVmax was associated with a high PLR; 2) a high PLR was associated with poor prognostic factors, including large tumor size, the presence of node metastasis, the presence of vascular invasion, a high NLR and a high SUVmax; 3) the PLR, but not the NLR, was an independent factor associated with a high SUVmax; 4) the PLR was associated with the SUVmax, but not with recurrent disease in patients with breast cancer. Our results suggest that the FDG uptake is associated with a high PLR and may be predictive of inflammation in addition to aggressive features among patients with breast cancer.

Table I. *Patient characteristics and clinicopathological features associated with F18-fluorodeoxyglucose (FDG) uptake in primary tumor. without FDG uptake in primary tumor.*

	FDG uptake		
	Low (n=70)	High (n=73)	*p*-Value
Age (y.o.)	60.3±11.3	57.6±12.5	0.906
Tumor size of invasion (mm)	14.4±9.1	23.0±9.9	<0.001
Node metastases positive (n)	11	21	0.095
ER positive (n)	63	58	0.064
PgR positive (n)	53	55	0.886
HER2 positive (n)	8	17	0.049
Nuclear grade 3 (n)	14	42	<0.001
ly positive (n)	17	41	<0.001
v positive (n)	5	23	<0.001
PLR	128.7±40.3	158.5±60.6	<0.001
NLR	2.08±0.91	2.83±1.65	<0.001
CEA	2.26±1.67	2.61±2.97	0.191
CRP	0.05±0.06	0.20±0.73	0.046

Values are expressed as mean±SD. N: Number; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ly: lymphatic invasion; v: vascular invasion; PLR: plateletlymphocyte ratio; NLR: neutrophil-lymphocyte ratio; CRP: C-reactive protein; CEA: carcinoembryonic antigen.

Table II. *Patient characteristics and clinicopathological features associated with platelet/lymphocyte ratio (PLR) in patients with breast cancer.*

	PLR		
	Low (n=69)	High (n=74)	*p*-Value
Age (y.o.)	60.7±10.8	57.3±12.9	0.096
Tumor size of invasion (mm)	16.9±9.5	20.5±11.0	0.019
Node metastases positive (n)	11	26	0.015
ER positive (n)	60	61	0.303
PgR positive (n)	52	56	0.880
HER2 positive (n)	13	12	0.847
Nuclear grade 3 (n)	27	29	0.870
ly positive (n)	27	31	0.868
v positive (n)	9	19	0.045
SUVmax	2.53±1.94	4.04±3.09	<0.001
NLR	1.88±0.58	3.02±1.69	<0.001
CEA	2.19±1.37	2.67±3.02	0.235
CRP	0.16±0.72	0.92±0.32	0.424

Values are expressed as mean±SD. N: Number; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ly: lymphatic invasion; v: vascular invasion; SUVmax: maximum standardized uptake value; NLR: neutrophillymphocyte ratio; CEA: carcinoembryonic antigen; CRP: C-reactive protein.

The PLR is determined the platelet/lymphocyte ratio and indicates inflammation. An elevated PLR is associated with adverse survival probabilities in multiple cancers, including breast cancer. However, evidence of the prognostic role of the PLR in breast cancer is relatively controversial (15, 31). Inflammation is associated with many factors, and an elevated PLR is not induced only by inflammation; it may also be induced by the cancer environment.

A high platelet count was considered to be related to metastasis of breast cancer, with a mechanism contributing to lysophosphatidic acid-dependent metastasis (15, 32). Platelets may also promote tumor angiogenesis and stroma formation by secreting vascular endothelial growth factor (VEGF) and facilitating the migration of inflammatory cells (15, 33, 34). VEGF is an established angiogenic factor, and the additional contribution of VEGF signaling to tumor immunity has gained significant attention (35). The lymphocytes also play an important role in cell-mediated anti-tumor immune responses and tumor immunological surveillance (15). The PLR may thus be associated with tumor immunological features. Cancer progression and prognosis are affected by many factors, including the host's inflammatory response and the immunological response in the tumor microenvironment (1, 2).

The SUVmax is used as a semiquantitative indicator of the FDG uptake, as the SUVmax is influenced by many factors, including the glucose transporter expression, viable cell number, tumor perfusion, and inflammatory cells (17, 21, 36). In our previous study, the FDG uptake was associated with a high NLR (which represents systemic inflammation): a high FDG uptake was associated with poor prognosis (8). However, FDG-PET measures the local glucose metabolism and may reflect local inflammation of cancer. For the evaluation of breast cancer, it is important to understand not only the systemic inflammatory response but also the local inflammatory response represented by FDG avidity.

Our present findings demonstrated that the PLR is associated with poor prognostic factors including a high SUVmax in addition to the inflammatory reaction; the SUVmax may represent the local reaction of the tumor. Based on our findings, in patients with breast cancer a high SUVmax with a high PLR may reflect aggressive tumor features and local inflammation, which may reflect the tumor microenvironment or immunoreaction to the tumor. A high NLR may predict systemic inflammation, which strongly predicts a poor prognosis. We thus propose that the combination of SUVmax and PLR findings is effective for predicting 1) local tumor microenvironment rather than the systemic environment and 2) the prognoses of patients with breast cancer.

This study has several potential limitations, including its retrospective design and the relatively small number of patients (n=143). Additional research is needed to explore other benefits and drawbacks of the PLR and the FDG-PET evaluations of primary breast cancer. To the best of our knowledge, this is the first report to describe the relationship between FDG uptake

and the PLR in breast cancer. The additional usefulness of the PLR as a predictor in primary breast cancer patients with high SUVmax values may indicate the status of the tumor microenvironment in patients with breast cancer.

In conclusion, in the present series of patients with breast cancer, a high PLR was independently associated with a high SUVmax, which is a strong poor prognostic factor. However, the PLR was not associated with recurrent disease in the patients. A high SUVmax and/or a high PLR in a breast cancer patient may reflect the tumor microenvironment. Further studies are warranted to evaluate how the combination of the FDG-uptake and PLR influences the tumor microenvironment and disease recurrence.

Conflicts of Interest

The Authors declare that they have no competing financial interests regarding this study.

Authors' Contributions

TF analyzed data and wrote the initial draft of the manuscript. ST, YN, SG, SO, and RY collected data and were involved in the initial study conception and design. ST, YN, SG, SO, RY, and SK were involved in drafting and revising the manuscript. All Authors have read and approved the final manuscript.

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