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# Predictive Factors for Non-sentinel Nodal Metastasis in Patients With Sentinel Lymph Node-positive Breast Cancer

YUMIKO ISHIZUKA[1], YOSHIYA HORIMOTO[1,2], MEI NAKAMURA[1,3], ATSUSHI ARAKAWA[2], TOMOYUKI FUJITA[4], KOTARO IIJIMA[1] and MITSUE SAITO[1]

[1]*Department of Breast Oncology, Juntendo University School of Medicine, Tokyo, Japan;*
[2]*Department of Human Pathology, Juntendo University School of Medicine, Tokyo, Japan;*
[3]*Department of Surgery, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan;*
[4]*Department of Breast Oncology, Juntendo University Urayasu Hospital, Urayasu, Japan*

**Abstract.** *Background: Axillary dissection is routinely conducted for all patients with sentinel node (SN)-positive breast cancer. Metastasis to non SNs is not often found after axillary dissection in patients with SN-positive breast cancer. Thus, we investigated clinicopathological features, including immune cells in peripheral blood, in order to identify factors related to metastasis to non-SNs. Patients and Methods: We retrospectively investigated 184 patients with SN-positive disease, treated at our institution during the 2013 through 2018 period. All clinicopathological data were obtained before and during surgery. Results: Metastasis to non SNs was observed in 64 cases (35%). The platelet-to-lymphocyte ratio (PLR) and the number of SN metastases were independent of metastasis to non SNs (p=0.023 and p=0.017, respectively). Patients with metastasis to non SNs had significantly lower PLR and more SN metastases. High lymphocyte number and low platelet number resulted in a low PLR. Conclusion: PLR might be a marker of metastasis to non SNs.*

Axillary lymph node status is one of the most important prognostic factors for patients with breast cancer (1) and determining the nodal status is crucial for selecting subsequent systemic treatments. Axillary dissection was formerly conducted for all patients but sentinel node (SN) biopsy was established in the 1990s as the standard procedure for patients with clinically N0 disease, making axillary dissection unnecessary (2, 3). Since then, axillary dissection has routinely been conducted for SN-positive cases. However, recent randomized trials found that some patients with SN-positive disease do not need axillary dissection. In patients having only micro-metastasis in the SN, omitting axillary dissection should now be recommended if systemic treatments are to be administered after surgery (4, 5). Moreover, according to clinical studies, axillary dissection can be avoided even in patients with macro-metastasis in the SN, if certain criteria, such as harboring very few positive SNs, are met (6, 7). However, whether this approach is feasible in routine clinical practice remains controversial.

*Attempt to predict metastasis to non SNs*. In practice, when the SN is intraoperatively found to be positive, the patient undergoes axillary dissection of regional lymph nodes (*i.e.* non-sentinel lymph nodes) and the status of lymph node involvement is determined at the final pathological assessment after surgery. However, metastasis to non SNs is often absent after axillary dissection in patients with SN-positive disease, although a previous study reported that approximately half of SN-positive cases had metastasis to non SNs (8). Hence, predicting metastasis to non SNs is important from the viewpoint of determining appropriate indications for axillary dissection. Several factors, such as tumor size, multiple lesions, lymphovascular involvement, and the number of SN metastases (9-12), have been described as being related to metastasis to non SNs. However, no predictive factors have as yet been established.

*Evaluation of immune cells in peripheral blood*. The relationships between immune cells in peripheral blood and the outcomes of patients with a variety of cancer types have been extensively investigated (13-16). The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been established as prognostic markers for patients with breast cancer (14, 16). High NLR and PLR are frequently reported to be related to poor outcomes. Studies

*Correspondence to:* Yoshiya Horimoto, Department of Breast Oncology, Juntendo University School of Medicine 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: horimoto@juntendo.ac.jp

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have suggested these markers to be predictive of treatment responses (17, 18) and we also recently reported high NLR to be related to poor responsiveness to eribulin-based regimens in patients with metastatic breast cancer (19). However, the mechanisms underlying these associations remain unknown, while neutrophils and platelets are considered to be markers for cancer-related inflammation and lymphocyte activity might reflect the immune system status (20, 21).

Based on these background factors, we hypothesized that these markers, NLR and PLR, might be higher in patients with more lymph node involvement. This would reflect the immune system failing against the cancer. We thus examined such immune cells in peripheral blood obtained before surgery.

We investigated clinicopathological features based on information obtained before and during surgery, including immune cells in peripheral blood, to identify factors related to metastasis to non SNs.

## Patients and Methods

*Patients*. In total, 1,599 patients underwent curative surgery with intraoperative SN biopsy at Juntendo University Hospital during the January 2013 through December 2018. Among them, 292 patients were diagnosed as having SN-positive disease. We excluded patients who received pre-operative systemic chemotherapy, had only ductal carcinoma *in situ*, did not undergo axillary dissection with micro-metastasis in SN or lacked necessary preoperative clinical data, such as hematological values. Thus, 184 SN-positive cases in total were investigated in this study. All patients were Asian women and had been diagnosed as having clinically N0 disease before surgery, based on pre-operative imaging.

This study was carried out with approval from the Ethics Committee of Juntendo University Hospital (no.: 16-096) and all data were collected after obtaining informed consent from the patients.

*Procedure of SN biopsy*. SN biopsy was intraoperatively conducted employing a combination of radiocolloid and blue dye injection methods. The day before surgery, first, $^{99m}$Tc futic acid was injected into the sub-areolar region, followed by indigo carmine blue injection into the same region. All 'hot' nodes detected by a gamma probe and/or blue lymph nodes were examined as SN with intraoperative pathological assessment. If any SN was found to be positive for metastases, further axillary lymph node dissection was performed. All non-SNs were submitted for routine pathological examination.

*Pathological examination*. Pathological examinations were carried out on biopsy specimens by two experienced pathologists at our hospitals. Tumor grade was judged based on the modified Bloom–Richardson histological grading system (22). On immunohistochemistry, estrogen receptor (ER) and progesterone receptor (PR) statuses were assessed semi-quantitatively and reported as positive when more than 1% of the nuclei of cancer cells showed staining. Human epidermal growth factor receptor 2 (HER2) expression was judged to be positive when strong staining of the complete membrane was observed in >10% of tumor cells. Regarding the Ki67 labelling index, a 'hot spot' was chosen under 200× magnification and cells positive for nuclear Ki67 were then counted. Tumor-infiltrating lymphocytes (TIL) were determined using hematoxylin and eosin-stained tumor biopsy sections, based on recommendations made by an International TILs Working Group (23). Briefly, TILs in the stromal compartment (% stromal TILs), employing the area of stromal tissue as a denominator, were semi-quantitatively determined with 10% increments. Average TIL numbers in the tumor area, not focusing on hot spots, were determined.

Since the purpose of the current study was to predict metastasis to non SNs based on information obtained before and during surgery, all pathological and immunohistochemical data were obtained using biopsy specimens.

*Evaluation of immune cells in peripheral blood*. Peripheral blood samples were obtained before surgery and the number of lymphocytes, NLR, PLR and the monocyte-to-lymphocyte ratio (MLR) were calculated from the laboratory data. Hematological analysis according to the flow cytometric method for measuring and differentiating cell types in whole blood was conducted using XE-5000 (Sysmex Corporation, Kobe, Japan) at Juntendo University hospital.

*Statistical analysis*. Statistical analyses were performed using JMP 14.2 statistical software (SAS Institute Inc., Cary, NC, USA). A logistic regression model was constructed in an attempt to discover the factors predicting metastasis to non SNs. For the full-model analysis, we first selected variables according to their clinical significance. Age, clinical tumor size, tumor grade, ER, HER2, biopsy specimen TIL, NLR, PLR and the number of SN metastases were thus chosen. For comparisons of mean values, such as those for age and NLR, unpaired Student's *t*-test was employed. A value $p<0.05$ was considered to indicate a statistically significant difference.

## Results

*Burden of SN metastasis and low PLR are related to metastasis to non SNs*. Metastasis to non SNs was observed in 64 cases, defined as the non-SN group, 35% of all 184 cases. Relationships between the presence of metastasis in non-SN cases and the factors examined are shown in Table I. There were six cases in which only *in situ* disease was observed in biopsy specimens of the primary tumor (invasive disease was confirmed in surgical specimens in all such cases) and all six were free of metastasis to non SNs ($p=0.022$). Patients in the group with metastasis to non SNs had significantly lower PLR ($p=0.037$). Moreover, the rates of metastasis to non SNs were significantly lower in cases in which only micro-metastasis was observed in SNs than in those with macro-metastasis in SNs ($p=0.041$). The number of metastases in SNs was 1.38 in the group with metastasis to non SNs, significantly more than the 1.17 in the non-SN group ($p=0.018$). The rate of metastasis to non SNs was actually dependent on the burden of SN metastasis (Figure 1A). Other factors, including the clinical size of the primary

Table I. *Metastasis to non sentinel node (SN) status and clinicopathological factors in the 184 study patients with node-positive breast cancer.*

| Variable | Metastasis to non SN, n | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|
| | Positive (n=64) | Negative (n=120) | OR | 95% CI | *p*-Value | OR | 95% CI | *p*-Value |
| Age, n | | | | | | | | |
| ≤50 Years | 33 | 64 | 0.93 | 0.51-1.71 | 0.819 | 0.81 | 0.35-1.90 | 0.630 |
| >50 Years | 31 | 56 | | | | | | |
| BMI | | | | | | | | |
| ≤25 kg/m$^2$ | 51 | 101 | 0.74 | 0.34-1.64 | 0.449 | | | |
| >25 kg/m$^2$ | 13 | 19 | | | | | | |
| Tumor size, n | | | | | | | | |
| cT0/1 | 31 | 56 | 1.07 | 0.58-1.97 | 0.819 | 1.79 | 0.81-4.03 | 0.148 |
| cT2/3 | 33 | 64 | | | | | | |
| Multiple lesions, n | | | | | | | | |
| Yes | 13 | 29 | 0.80 | 0.37-1.65 | 0.550 | | | |
| No | 51 | 91 | | | | | | |
| Histology, n | | | | | | | | |
| Invasive carcinoma | 64 | 114 | 6.11e$^6$ | 1.46-∞ | **0.022** | | | |
| DCIS | 0 | 6 | | | | | | |
| Histology of invasive carcinoma, n | | | | | | | | |
| IDC (NST) | 56 | 102 | 0.82 | 0.32-2.21 | 0.691 | | | |
| Other | 8 | 12 | | | | | | |
| Tumor grade, n | | | | | | | | |
| High | 2 | 10 | 0.37 | 0.06-1.47 | 0.171 | 0.25 | 0.02-1.91 | 0.186 |
| Low/moderate | 57 | 106 | | | | | | |
| Unknown | 5 | 4 | | | | | | |
| Ki67 LI | | | | | | | | |
| >30% | 15 | 46 | 0.51 | 0.25-1.03 | 0.060 | | | |
| ≤30% | 37 | 58 | | | | | | |
| ER, n | | | | | | | | |
| Positive | 59 | 108 | 1.09 | 0.37-3.64 | 0.876 | 1.05 | 0.24-5.25 | 0.952 |
| Negative | 5 | 10 | | | | | | |
| PR, n | | | | | | | | |
| Positive | 53 | 105 | 0.55 | 0.23-1.35 | 0.189 | | | |
| Negative | 11 | 12 | | | | | | |
| HER2, n | | | | | | | | |
| Positive | 8 | 7 | 2.24 | 0.77-6.71 | 0.137 | 3.14 | 0.65-19.29 | 0.158 |
| Negative | 56 | 110 | | | | | | |
| TIL, % | | | | | | | | |
| Mean±SD | 26±21 | 22±17 | 2.53* | 0.46-14.3 | 0.283 | 3.22* | 0.44-26.45 | 0.252 |
| Lymphocyte count, n/μl | | | | | | | | |
| Mean±SD | 1820±506 | 1710±493 | 3.03* | 0.65-14.5 | 0.156 | | | |
| NLR | | | | | | | | |
| Mean±SD | 2.09±0.92 | 2.19±1.12 | 0.53* | 0.06-4.08 | 0.550 | 0.54* | 0.03-9.15 | 0.659 |
| PLR | | | | | | | | |
| Mean±SD | 138.6±42.1 | 157.3±67.5 | 0.09* | 0.008-0.88 | **0.037** | 0.05* | 0.00309-0.68 | **0.023** |
| MLR | | | | | | | | |
| Mean±SD | 0.168±0.060 | 0.171±0.058 | 0.72* | 0.11-4.41 | 0.724 | | | |
| SN metastasis, n | | | | | | | | |
| Micro-metastasis | 1 | 10 | 0.17 | 0.009-0.94 | **0.041** | | | |
| Macro-metastasis | 63 | 110 | | | | | | |
| Number of SN metastases | | | | | | | | |
| Mean±SD | 1.38±0.72 | 1.17±0.44 | 1.93** | 1.12-3.51 | **0.018** | 2.95** | 1.22-7.75 | **0.017** |

BMI: Body mass index; LI: labeling index; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; TIL: tumor-infiltrating lymphocytes; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; SN: sentinel node; DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; NST: non-special type; OR: odds ratio; CI. confidence interval. *Range of the odds ratio; **unit of the odds ratio. Statistically significant *p*-values are shown in bold.

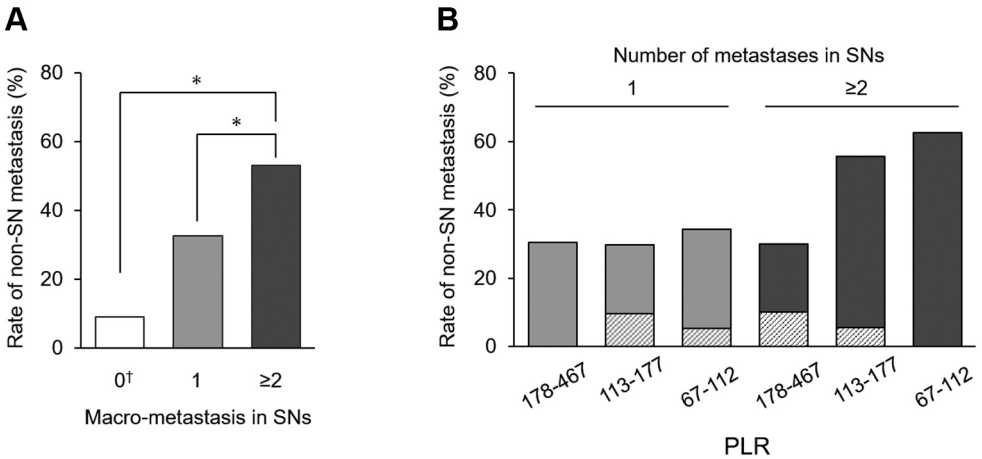


Figure 1. *Rates of metastasis to non sentinel nodes (SNs) according to metastatic burden. A: The rates of metastasis to non sentinel nodes (SNs) were compared according to the number of macro-metastases in SNs. †Cases with SN micro-metastasis only. *Significantly different at p<0.05. B: The rates of metastasis to non SNs according to platelet-to-lymphocyte ratio (PLR) are shown for cases according to the number of metastases in SNs. Oblique lines indicate cases with micro-metastases only in SNs.*

tumor and tumor grade, were not related to metastasis to non SNs. On multivariate analysis, PLR and the number of SN metastases remained as factors independently related to metastasis to non SNs ($p$=0.023 and $p$=0.017, respectively).

Furthermore, we calculated the rates of metastasis to non SNs in combinations of these two independent factors, PLR and the number of SN metastases, employing the upper and lower quantile values for PLR. An inverse relationship between metastasis to non SNs and PLR was observed in patients who had two or more SN metastases (Figure 1B), although the differences were not statistically significant.

*Predictive model for metastasis to non SNs*. Based on the aforementioned multivariate analysis, we attempted to establish a model predicting metastasis to non SNs, employing two factors (PLR and the number of metastases in SN). The logistic regression model was applied employing and the receiver operating characteristic (ROC) curve was drawn (Figure 2). The area under the curve (AUC) of this curve was 0.611, suggesting the discriminative capacity of our model to be low. Moreover, we judged the scale of our dataset as not being large enough for establishing an appropriate predictive model because more than 100 events are generally regarded as being needed to conduct a validation study.

*High numbers of lymphocytes and low platelet numbers result in low PLR*. Our data showed PLR and NLR to both be lower in the group with metastasis to non SNs than in that without, although the difference in NLR did not reach statistical significance (Table I). Thus, we further investigated the source of these differences, lymphocytes or platelets and neutrophils

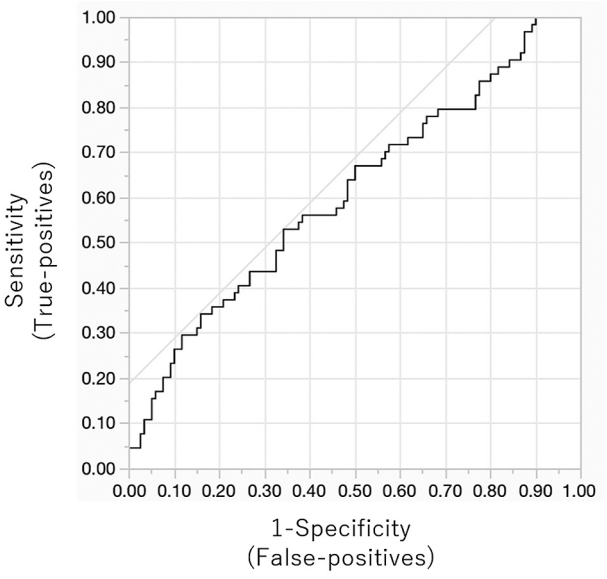


Figure 2. *Receiver operating characteristics curve constructed employing platelet-to-lymphocyte ratio and the number of metastases in sentinel nodes. The area under the curve was 0.611.*

(*i.e.* a high absolute number of lymphocytes or low platelet/neutrophil numbers). Comparisons of absolute numbers of lymphocytes, platelets and neutrophils according to the presence of metastasis to non SNs are shown in Figure 3. Lymphocyte counts were higher in the group with metastasis to non SNs, while the number of platelets was lower, although these differences were not statistically significant. These data suggest that differences in both lymphocytes and platelets,

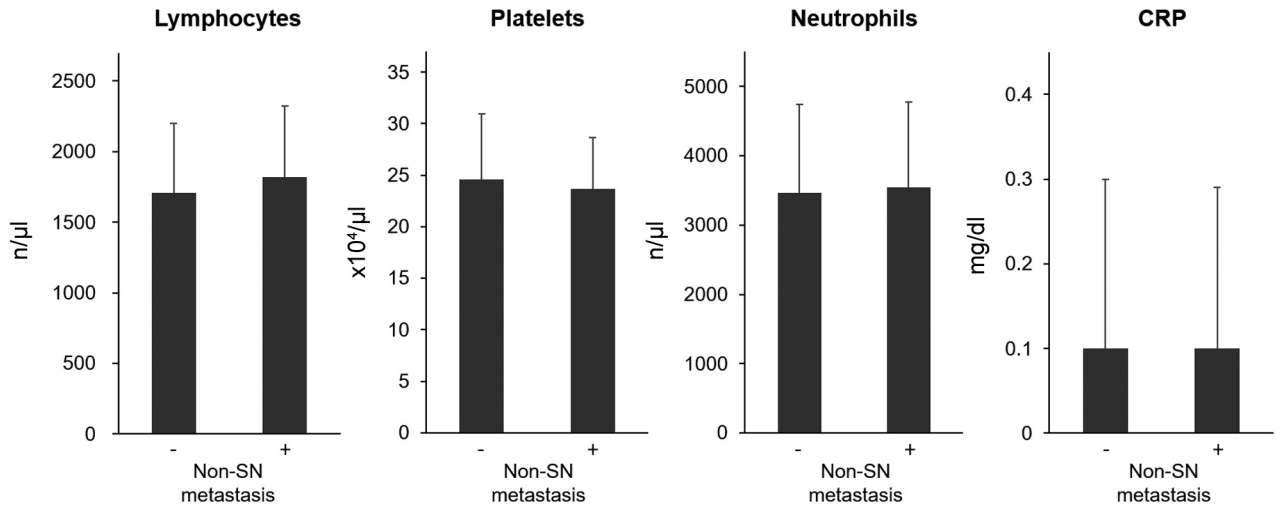


Figure 3. *Comparison of peripheral blood data according to the presence of metastasis in non sentinel nodes (SNs). Absolute numbers of lymphocytes, platelets and neutrophils, and C-reactive protein (CRP) levels were compared between the groups without (n=120) and with (n=64) non-SN metastasis.*

Table II. *Clinicopathological features of 200 patients with sentinel node (SN)-negative breast cancer in comparison with the 184 patients of the SN-positive study group.*

| Variable | | SN-negative cases | SN-positive cases | *p*-Value |
|---|---|---|---|---|
| Age, years | Mean±SD | 55.4±12.6 | 53.9±12.6 | 0.252 |
| Tumor size, n (%) | pT1 | 139 (70%) | 81 (44%) | <0.001* |
| | pT2 | 56 (28%) | 87 (47%) | |
| | pT3 | 5 (2%) | 16 (9%) | |
| Histology of invasive carcinoma, n (%) | IDC (NST) | 185 (93%) | 164 (89%) | 0.252 |
| | Other | 15 (7%) | 20 (11%) | |
| Tumor grade, n (%) | High | 29 (15%) | 19 (10%) | 0.228 |
| | Low/moderate | 163 (81%) | 156 (85%) | |
| | Unknown | 8 (4%) | 9 (5%) | |
| Ki67 LI | Mean±SD | 30.9±23.2 | 38.4±23.9 | 0.002 |
| ER, n (%) | Positive | 177 (89%) | 167 (91%) | 0.469 |
| | Negative | 23 (11%) | 17 (9%) | |
| PR, n (%) | Positive | 167 (84%) | 158 (86%) | 0.520 |
| | Negative | 33 (16%) | 26 (14%) | |
| HER2, n (%) | Positive | 25 (13%) | 19 (10%) | 0.504 |
| | Negative | 175 (87%) | 165 (90%) | |

LI: Labeling index; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; SN: sentinel node; IDC: invasive ductal carcinoma; NST: non-special type. All pathological data shown here were based on surgical specimens. *pT1 *vs*. pT2/3.

rather than one of these factors alone, contributed to the significantly lower PLR in the group with metastasis to non SNs. The number of neutrophils and the level of C-reactive protein, a major marker of inflammation, also did not differ significantly between these two groups.

For comparison, we next randomly chose 200 patients with SN-negative disease who underwent curative surgery without pre-surgical systemic chemotherapy during the same period and collected the data of these patients. Clinicopathological features are presented in Table II. These patients had smaller tumors, with low Ki67 labelling index, than did the 184 SN-positive cases. Comparisons of PLR, lymphocytes and platelets between there patients are shown in Figure 4. No statistically significant differences were observed for any of the variables but there was a tendency for patients with SN-negative disease to have peripheral

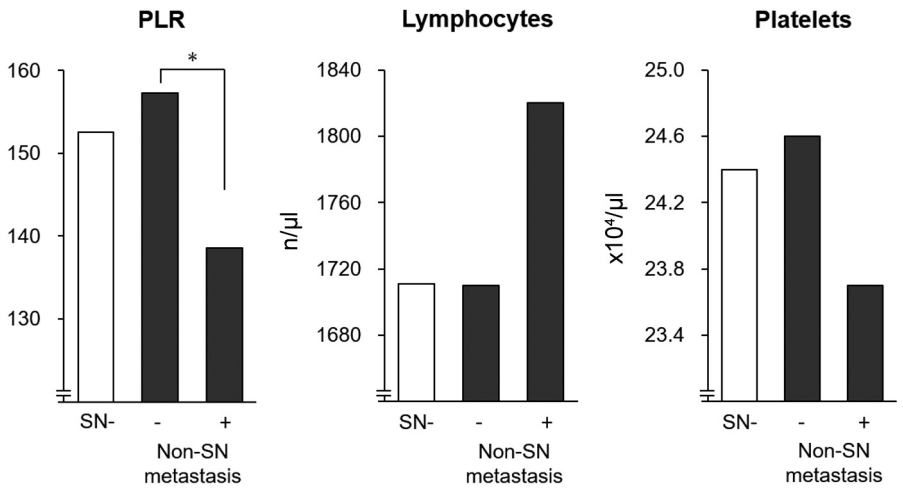


Figure 4. *Comparison of peripheral blood data between patients with sentinel node-negative (SN−) disease (n=200) and those with SN-positive disease with (+) and without (−) non SN metastasis. *Significantly different at p<0.05. The minimum values on the y-axis were adjusted to allow the differences to be visualized clearly.*

blood data similar to that of the SN-positive cases without metastasis to non SNs.

## Discussion

We revealed significant PLR reductions in the group with metastasis to non SNs. Interestingly, this observation was the opposite of what we had originally hypothesized. As mentioned above, PLR is an established prognostic marker for breast cancer and high PLR is frequently reported to be related to poor patient outcomes (24, 25). However, the mechanism underlying these associations has not yet been elucidated. As an independent marker, the absolute lymphocyte count has been investigated in more detail than the platelet count. High lymphocyte counts are reportedly associated with good responses to chemotherapies in patients with breast cancer (26), while lymphopenia has been regarded as an indicator of poor outcomes (13). For platelets, one study reported that a high platelet count was related to worse prognosis in other cancer types (27). Moreover, an interaction with cancer cells at the molecular level has been a research focus and platelet activation is speculated to promote cancer progression (28, 29). However, assessment of patient outcomes based on only a single marker presents difficulty considering that numerous studies have employed various combinations including NLR, PLR and MLR across different types of malignant tumor. Our data suggest that differences in both lymphocytes and platelets contributed to the low PLR in the group with metastasis to non SNs and the profiles of these markers were similar in those without such metastasis and SN-negative disease (Figures 2 and 3). We thus speculate that the lymphocyte increase in the peripheral blood of patients with metastasis to non SNs might have occurred as a host immune system response to progression of the cancer to these nodes. Nevertheless, differences in these markers were small and further studies, designed to compare patients with and without metastasis to non SNs with healthy women and patients with clinically node-positive breast cancer are also necessary to obtain conclusive evidence.

There was no difference in TILs between patients with and without metastasis to non SNs in the current study (Table I). As a means of predicting non-SN status, peripheral blood might be more suitable than assessment of local immune-responses such as TIL.

We found the number of metastases in SNs to be significantly related to metastasis to non SNs , an observation consistent with a previous report (9). On the other hand, several studies have suggested other factors such as tumor size and the presence of multiple lesions to predict metastasis to non SNs (10-12) but such relationships were not demonstrated by this study. One of the reasons for this might be that we did not recruit SN-negative cases to participate in the current study. Another reason might be that we employed pre- and intra-operatively available information, with consideration of clinical application, while most previous studies included the final pathological findings based on surgical specimens. Taken together, our findings indicate that the number of metastases might be a very strong factor predicting metastasis to nodes other than SNs.

Major limitations of the current study include the small number of cases and the lack of a validation study. Further investigations, including a prospective study with a larger number of patients, are needed.

Our data suggest PLR to have potential as a marker for metastasis to non SNs. To the best of our knowledge, this is the first study to show the relationship between PLR and metastasis to non SNs. Furthermore, PLR status in patients with SN-positive disease appears to merit further investigation in terms of cancer biology.

## Conflicts of Interest

The Authors have no conflicts of interest to declare.

## Authors' Contributions

YI contributed to the design, acquisition of samples, and writing of the article. YH contributed to the design, analysis of data, and writing of the article. MN and KI contributed to acquisition of samples. YH and AA conducted histological assessment. TF and MS reviewed and edited. All Authors contributed to discussions and agreed on the final version of the submitted article.

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