Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy

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Blood-based biomarkers reflect systemic inflammation status and have prognostic and predictive value in solid malignancies. As a recently defined biomarker, Pan-Immune-Inflammation-Value (PIV) integrates different peripheral blood cell subpopulations. This retrospective study of collected data aimed to assess whether PIV may predict the pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in Turkish women with breast cancer. The study consisted of 743 patients with breast cancer who were scheduled to undergo NAC before attempting cytoreductive surgery. A pre-treatment complete blood count was obtained in the two weeks preceding NAC, and blood-based biomarkers were calculated from absolute counts of relevant cell populations. The pCR was defined as the absence of tumor cells in both the mastectomy specimen and lymph nodes. Secondary outcome measures included disease-free survival (DFS) and overall survival (OS). One hundred seven patients (14.4%) had pCR. In receiver operating characteristic analysis, optimal cut-off values for the neutrophile-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte (PLR), PIV, and Ki-67 index were determined as ≥ 2.34, ≥ 0.22, ≥ 131.8, ≥ 306.4, and ≥ 27, respectively. The clinical tumor (T) stage, NLR, MLR, PLR, PIV, estrogen receptor (ER) status, human epidermal growth factor receptor-2 (HER-2) status, and Ki-67 index were significantly associated with NAC response in univariate analyses. However, multivariate analysis revealed that the clinical T stage, PIV, ER status, HER-2 status, and Ki-67 index were independent predictors for pCR. Moreover, the low PIV group patients had significantly better DFS and OS than those in the high PIV group (p = 0.034, p = 0.028, respectively). Based on our results, pre-treatment PIV seems as a predictor for pCR and survival, outperforming NLR, MLR, PLR in predicting pCR in Turkish women with breast cancer who received NAC. However, further studies are needed to confirm our findings.

Malignancies arising in the mammary gland are the most common type of cancer in women1. The lifetime risk of breast cancer for a woman has been calculated at around 1-in-7 to 1-in-102, indicating that approximately 10% of the female population will be diagnosed with breast cancer during their lifetime13. Neoadjuvant chemotherapy (NAC)—consisting of chemotherapy delivered before local treatment (surgery)—has become the standard of care in patients with locally advanced breast cancer1. In addition, downstaging of the primary tumor in patients with earlier stages of breast cancer may facilitate breast-conserving therapy and offer the opportunity to downstage the axilla—ultimately obviating the need for axillary treatment in some patients14,15. The overarching goal of NAC is to achieve pathological complete response (pCR)—which is, in turn, associated
with a lower recurrence rate and more favorable survival outcomes⁶. Unfortunately, there is considerable inter-individual variation in response to NAC amongst women with breast cancer, and several variables have been investigated in relation to this variability⁷.

In the last two decades, the relationship between chronic inflammation and cancer has become very popular, and both the diagnostic and therapeutic value of inflammatory markers have been studied extensively. Inflammation has been shown to promote tumor initiation and progression, whereas escape from immune surveillance may favor cancer invasiveness⁸. In the tumor microenvironment, neutrophils, monocytes-derived macrophages, and platelets have adverse prognostic significance by promoting tumoral angiogenesis and tumor growth, whereas tumor-infiltrating lymphocytes portend favorable outcomes⁹–¹¹. Based on the assumption that peripheral blood cell populations can provide information about the intratumoral immune system status, peripheral blood-derived inflammation markers such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) was shown to have prognostic value in many solid organ malignancies¹²–¹⁴. In addition to their prognostic value, these markers were reported to predict the neoadjuvant chemotherapy response in breast cancer¹⁵–¹⁷.

In 2020, Fuca et al. reported that a novel systemic immune score called Pan-Immune-Inflammation-Value (PIV) performed better in predicting survival outcomes than other immune-inflammatory biomarkers such as NLR in advanced colorectal cancer patients⁶⁶. However, PIV’s predictive and prognostic value in breast cancer patients receiving NAC has not been studied. We, therefore, designed the current study to address these issues specifically.

**Results**

The general characteristics of the entire study sample (n = 743) are shown in Table 1. The median age was 48.0 years (range: 22.0–83.5 years). One hundred ninety-seven patients (26.5%) had T3/T4, and 37.5% had node-positive disease. More than two-thirds received chemotherapy regimens containing both anthracycline and taxane. Of patients, 14.4% had pCR.

Table 2 presents the values of the area under the curve, sensitivity, and specificity in receiver operating characteristic (ROC) analysis. The cut-off values for the NLR, MLR, PLR, PIV, and Ki-67 index were determined as ≥ 2.34, ≥ 0.22, ≥ 131.8, ≥ 306.4, and ≥ 27, respectively.

**Outcomes.** Table 3 depicts the analyses of the association between the patients’ characteristics and pCR. The clinical tumor (T) stage, NLR, MLR, PLR, PIV, estrogen receptor (ER) status, human epidermal growth factor receptor-2 (HER-2) status, and Ki-67 index were significantly associated with response to NAC. However, multivariate logistic regression analysis revealed that the clinical T stage (odds ratio [OR], 2.16; 95% confidence interval [CI], 1.10–4.23, p = 0.025), PIV (OR, 3.32; 95% CI, 1.53–7.21, p = 0.002), ER status (OR, 3.24; 95% CI, 1.84–5.71; p < 0.001), HER-2 status (OR, 3.84; 95% CI, 2.17–6.80; p < 0.001), and Ki-67 index (OR, 3.30; 95% CI, 1.72–6.32; p < 0.001) were independent predictors for pCR (Table 4). The blood-derived inflammation markers other than PIV lost statistical significance in multivariate analysis.

The median follow-up time was 67.5 months (range: 10.5–194.4 months). Median DFS and OS were not reached. 12-, 36-, and 60-months disease-free survival rates were 94.6%, 84.6%, 77.5%, respectively. 12-, 36-, and 60-months overall survival rates were 99.6%, 95.4%, 88.7%, respectively. As a secondary outcome, the disease-free survival (DFS) of patients in the low PIV group was significantly longer than the DFS of the high PIV group patients (hazard ratio [HR], 0.69; 95% CI 0.49–0.97; p = 0.034; Fig. 1A). Similarly, the low PIV group patients had significantly better overall survival (OS) than those in the high PIV group (HR, 0.61; 95% CI 0.39–0.95; p = 0.028; Fig. 1B).

**Discussion**

In the present study, we demonstrated for the first time that a new inflammatory score, PIV, was one of the independent predictors for pCR to NAC like the well-studied other clinicopathological factors such as T stage, ER status, HER-2 status, and Ki-67 index in breast cancer. Additionally, PIV outperformed other blood-derived inflammation markers in predicting pCR, and it also had a prognostic value for DFS and OS.

In general, white blood cell count reflects an individual’s systemic and/or local inflammatory status¹¹. Neutrophils are known to regulate the tumor microenvironment and produce cytokines, chemokines, and growth factors that may promote angiogenesis as well as tumor cell proliferation and migration¹⁵. The M2 phenotype tumor-associated macrophages (TAMs) deriving from circulating monocytes exist within the tumor microenvironment and promote metastasis and immunosuppression²⁰,²¹. It was reported that peripheral monocyte count was associated with the density of the TAMs, and high absolute monocyte count predicted poor survival in cancer patients²²,²³. Platelets are other cells contributing to cancer-favored inflammation by various mechanisms. For example, the activated platelets inhibit the interaction between tumor cells and cytolytic immune cells by forming a layer around tumor cells and support tumor growth via the secretion of several factors such as TGF-β²⁴,²⁵. Hence, high platelet counts were reported to be associated with adverse outcomes in breast cancer²⁶. In contrast, lymphocytes are resistant for tumor-specific immune response—including T-lymphocyte tumor infiltration and cytotoxic T-lymphocyte-mediated antitumor activity¹¹,²⁷. Starting from these findings, NLR, MLR, and PLR, indexes reflecting the balance between inflammation and immunoreaction in cancer, were reported to have predictive value in NAC response in many breast cancer studies, supporting our findings of univariate analysis¹⁵–¹⁷,²⁸.

Although the scientific evidence supporting the predictive value of the blood-derived inflammation indexes has been expanding, there are conflicting reports about which index provides the best prediction for the efficacy of NAC in breast cancer²⁹–³¹. For example, Eren et al. reported that NLR was the only independent predictive
factor of pCR among blood-derived inflammation markers in multivariate analysis. In another study conducted by Peng et al., multivariate analysis of 808 breast cancer patients showed that the lymphocyte-monocyte ratio was the only independent predictive factor for the efficacy of NAC among these inflammatory markers. In addition, Hu et al. stated that PLR had superior efficacy to NLR in predicting NAC response. When these studies are evaluated together with scholars presenting negative results, it has emerged offering a combination of inflammation markers useful for predicting NAC response.

Table 1. Clinicopathological characteristics of the patients. T tumor, pCR pathological complete response, HER-2 human epidermal growth factor receptor-2. *Histopathological examination of the pre-treatment biopsy specimen. †Including lobular, mucinous, papillary, metaplastic, and mixed tumors.

| Characteristic                        | N (743) | (%)  |
|--------------------------------------|---------|------|
| **Age**                              | 48.0 (22.0–83.5) |
| **Menopausal status**                |         |      |
| Pre-menopausal                       | 379     | (51.0) |
| Post-menopausal                      | 364     | (49.0) |
| **Clinical T stage**                 |         |      |
| T1-T2                                | 518     | (69.7) |
| T3-T4                                | 197     | (26.5) |
| Missing                              | 28      | (3.8)  |
| **Clinical node status**             |         |      |
| Negative                             | 444     | (59.8) |
| Positive                             | 279     | (37.5) |
| Missing                              | 20      | (2.7)  |
| **Histotype***                       |         |      |
| Invasive ductal carcinoma            | 671     | (90.3) |
| Other histology types†               | 53      | (7.1)  |
| Missing                              | 19      | (2.6)  |
| **Estrogen receptor status**         |         |      |
| Positive                             | 484     | (65.1) |
| Negative                             | 184     | (24.8) |
| Missing                              | 75      | (10.1) |
| **HER-2 status***                    |         |      |
| Positive                             | 160     | (21.5) |
| Negative                             | 508     | (68.4) |
| Missing                              | 75      | (10.1) |
| **Ki-67 index (%)***                 |         |      |
| Median (range)                       | 26 (0–100) |
| **Chemotherapy regimens**            |         |      |
| Anthracycline plus taxane            | 510     | (68.6) |
| Anthracycline-based regimens         | 204     | (27.5) |
| Taxane-based regimens                | 29      | (3.9)  |
| **pCR**                              |         |      |
| Yes                                  | 107     | (14.4) |
| No                                   | 636     | (85.6) |

Table 2. Receiver operating characteristic curve analyses for pathological complete response. AUC the area under the curve, CI confidence interval, NLR neutrophil-to-lymphocyte ratio, MLR monocyte-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, PIV pan-immune-inflammation-value.
of these markers\textsuperscript{35,36}. The combination of NLR and PLR was reported to predict NAC response more precisely than NLR and PLR alone, claiming that the combination of different biomarkers could better define the patients’ inflammatory status\textsuperscript{35,36}.

PIV is a new blood-based biomarker integrating different peripheral blood immune cell subpopulations—neutrophil, platelet, monocyte, and lymphocyte. Due to its potential to represent comprehensively patient’s immunity and systemic inflammation, PIV was proposed as a stronger predictor of outcomes in advanced cancer patients receiving cytotoxic chemotherapy, immunotherapy, and targeted therapy\textsuperscript{18,37–39}. Recently, Ligorio reported that PIV was firmly associated with survival and outperformed NLR, PLR, and MLR in predicting survival in patients with HER-2 positive advanced breast cancer\textsuperscript{39}. In line with the studies mentioned above, we showed that patients with low PIV scores had better survival outcomes. Furthermore, to our knowledge, this is the first study reporting that PIV was a more reliable predictor of pCR after NAC than other blood-based markers in breast cancer patients.

Meta-analyses and systematic reviews have shown that numerous factors—including age, genetic polymorphisms, tumor-infiltrating lymphocytes, programmed death-ligand 1, ER, progesterone receptor, and HER2

| Characteristic | pCR | P value |
|---------------|-----|---------|
| Median age, years (minimum–maximum) | 49.5 (23.5–77.7) | 47.8 (22.8–83.5) | 0.694\textsuperscript{a} |
| Menopausal status, n (%) | | | 0.903\textsuperscript{b} |
| Premenopausal | 54 (50.5) | 325 (51.1) | |
| Postmenopausal | 53 (49.5) | 311 (48.9) | |
| Clinical T stage, n (%) | | | 0.019\textsuperscript{c} |
| T1/2 | 86 (81.9) | 432 (70.8) | |
| T3/4 | 19 (18.1) | 178 (29.2) | |
| Clinical Node status, n (%) | | | 0.681\textsuperscript{d} |
| Negative | 39 (42.0) | 240 (39.0) | |
| Positive | 67 (58.0) | 377 (61.0) | |
| NLR, n (%) | | | 0.015\textsuperscript{e} |
| Low | 74 (74.7) | 308 (61.8) | |
| High | 25 (25.3) | 190 (38.2) | |
| MLR, n (%) | | | 0.001\textsuperscript{f} |
| Low | 63 (63.6) | 229 (46.0) | |
| High | 36 (36.4) | 269 (54.0) | |
| PLR, n (%) | | | 0.001\textsuperscript{g} |
| Low | 72 (72.7) | 275 (55.2) | |
| High | 27 (27.3) | 228 (44.8) | |
| PIV, n (%) | | < 0.001\textsuperscript{h} |
| Low | 81 (81.8) | 270 (54.2) | |
| High | 18 (18.2) | 228 (45.8) | |
| ER status, n (%) | | < 0.001\textsuperscript{i} |
| Negative | 63 (60.6) | 121 (21.5) | |
| Positive | 41 (39.4) | 443 (78.5) | |
| HER-2 status, n (%) | | < 0.001\textsuperscript{j} |
| Negative | 55 (52.9) | 453 (80.3) | |
| Positive | 49 (47.1) | 111 (19.7) | |
| Ki-67 index, (%) | | < 0.001\textsuperscript{k} |
| Low | 17 (17.5) | 230 (46.9) | |
| High | 80 (82.5) | 260 (53.1) | |
| Histopathology, n (%) | | 0.265\textsuperscript{l} |
| Invasive ductal carcinoma | 101 (95.3) | 570 (92.2) | |
| Other histology types | 5 (4.7) | 48 (7.8) | |
| Chemotherapy, n (%) | | 0.423\textsuperscript{m} |
| Anthracycline plus taxane | 77 (72.0) | 433 (88.1) | |
| Other regimens | 30 (28.0) | 203 (11.9) | |

Table 3. Association between the patients’ characteristics and pCR. pCR pathological complete response, NLR neutrophil-to-lymphocyte ratio, MLR monocyte-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, PIV Pan-immune-inflammation-value, ER estrogen receptor, HER-2 human epidermal growth factor receptor-2. \textsuperscript{a}Mann-Whitney test; \textsuperscript{b}Pearson’s Chi-squared test. Data are given as counts (percentages) unless otherwise indicated. Bold numbers indicate statistical significance.
expression status—may be predictive of response to NAC in women with breast cancer. However, most of these variables become available only following detailed pathological and genetic investigations. There is, therefore, an urgent need for reliable prognostic tools grounded on simple pre-treatment variables. In this scenario, PIV—an easy-to-drive biomarker originating from routine complete blood count—may help clinicians to predict treatment responses after prospective validation and confirmation of our results by further studies.

Some limitations of our study merit comment, including the retrospective design, the presentation of single-center experience, and the inclusion of women of Turkish descent only. Furthermore, although we excluded the patients with hematological disorders and those receiving immunomodulatory treatment, various other conditions may influence the blood-based biomarkers.

Based on our results, pre-treatment PIV seems to have a significant predictive value and outperform NLR, MLR, PLR in predicting pCR in Turkish women with breast cancer who received NAC. In addition, PIV has a prognostic impact on survival. However, further studies are needed to confirm our findings.

Table 4. Univariate and multivariate logistic regression analysis for the predictors of pathological complete response. OR odds ratio, CI confidential interval, RC reference category, NLR neutrophil-to-lymphocyte ratio, MLR monocyte-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, PIV Pan-immune-inflammation-value, ER estrogen receptor, HER-2 human epidermal growth factor receptor-2, IDC invasive ductal carcinoma, AplusT anthracycline plus taxane. The multivariate logistic regression model is significant ($p < 0.001$). Bold numbers indicate statistical significance.

![Figure 1. Kaplan-Meier plots of survival endpoints in different Pan-Immune-Inflammation-Value (PIV) groups (low versus high): (A) disease-free survival; (B) overall survival.](image)

Materials and methods

Study population. Figure 2 shows the profile of our study. The electronic records of patients admitted to the Department of Oncology or the Department of General Surgery, Uludag University Medical Center (Bursa, Turkey) between January 2008 and December 2019 due to breast cancer were reviewed. Among patients who underwent NAC before attempting cytoreductive surgery, patients who were aged < 18 years, received immu-
nomodulatory treatment or neoadjuvant endocrine therapy, had a history of malignancies at other sites, hematological disease, incomplete data were excluded. The study consisted of 743 Turkish women.

**Data collection.** The following variables were extracted from medical records in all participants: age; menopausal status; pre-treatment T stage; pre-treatment axillary lymph node status; pre-treatment histotype; pre-treatment expression of ER, HER-2, and Ki-67; and chemotherapy regimens. By immunohistochemical staining, ER expression levels ≥ 1% were considered positive. The final pathological reports of all patients were reviewed for pCR. According to the American Joint Committee on Cancer (AJCC) Staging Manual, eighth edition, the staging of the patients was carried out. A pre-treatment complete blood count was obtained in the two weeks preceding NAC. The absolute counts of neutrophils, monocytes, platelets, and lymphocytes were used to estimate NLR, MLR, and PLR. The PIV was calculated by multiplying neutrophil count (10³/mL) by platelet count (10³/mL) and monocyte count (10³/mL) and dividing the result by lymphocyte count (10³/mL).

**Ethical statement.** The study protocol complied with the tenets of the Helsinki declaration, and ethical approval was granted by the Institutional Review Board of Bursa Uludag University (Approval Number: 2020-6/31). The Clinical Research Ethics Committee of the Bursa Uludag University Faculty of Medicine waived the need for informed consent due to the study's retrospective nature.

**Outcomes.** The primary outcome measure was pCR to NAC. The pCR was defined as the absence of tumor cells in both the mastectomy specimen and the sampled or dissected regional lymph nodes. Secondary outcome measures included DFS and OS. DFS was calculated as the time (in months) from curative surgery until recurrence or death, whichever occurred first. OS was calculated as the time (in months) from breast cancer diagnosis to death.

**Figure 2.** Flowchart of patients selection.
Statistical analysis. The optimal cut-off points for NLR, MLR, PLR, PIV, and Ki-67 index were determined using ROC curve analysis, taking pCR as the endpoint of interest. The general characteristics of the study patients are presented using descriptive statistics (median, ranges, counts, and percentages). The Pearson's Chi-squared test (categorical variables) or the Mann–Whitney U test (continuous variables) were used to analyze the association between pCR and the variables. Binary logistic regression analysis was employed for multivariate analysis, including the factors having a p-value below 0.25 in univariate analysis. Survival curves were plotted using the Kaplan–Meier method and compared with the log-rank test. All calculations were performed using SPSS, version 22.0 (IBM, Armonk, NY, USA) and MedCalc Statistical Software trial version 20.009 (MedCalc Software bv, Ostend, Belgium; www.medcalc.org; 2021). Two-tailed p values < 0.05 were considered statistically significant.

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**Author contributions**
A.B.S conceived the study design, A.B.S, G.Y., R.G., B.O, K.S., Z.B.Y., S.O.O., and U.H. collected the data, A.B.S. performed statistical analyses. A.B.S. and E.C. wrote the manuscript. T.E., A.D., S.T., M.S.G., and S.C. edited the manuscript. All authors have read and approved the final manuscript.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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