



Markers of inflammation as predictors of efficacy of trastuzumab therapy in HER2-positive metastatic breast cancer patients

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Inflammatory indexes correlate with the effectiveness of therapy and prognosis of many cancer types. Our study aimed to identify independent predictors of the efficacy of trastuzumab therapy affecting progression-free survival (PFS) and overall survival (OS) in patients with HER2-positive metastatic breast cancer (mBC). The retrospective study included 78 HER2-positive mBC patients treated with trastuzumab at Sumy Regional Clinical Oncology Center. The baseline clinicopathological characteristics including age, number of metastases, menopausal status, hormonal status, trastuzumab-containing regimen, and inflammatory indexes, such as neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR) and pan-immune-inflammation value (PIV), were collected. Cut-off values of inflammatory markers were determined by ROC analysis. $AUC \geq 0.7$ was considered statistically significant. Factors affecting PFS and OS were determined using the multivariate Cox proportional hazard model. Response to treatment was assessed every 2-3 cycles. Low PLR and trastuzumab plus chemotherapy regimen correlated with a high disease control rate. Multivariate analysis assessed the prognostic impact of age, number of metastases, menopausal status, hormonal status, trastuzumab-containing regimen, and inflammatory indexes on PFS and OS in HER2-positive mBC patients. Trastuzumab-containing regimen and PLR were independent predictors of PFS. Patients who received trastuzumab plus chemotherapy and whose PLR before treatment was low had significantly better PFS. For OS, multivariate analysis showed the same results. Low PLR and trastuzumab plus chemotherapy regimen were independent predictors of OS. Low PLR is associated with better PFS, OS, and a high disease control rate. PLR may be an effective marker for identifying the candidates who most benefit from trastuzumab. Compared with trastuzumab monotherapy, the combination of trastuzumab and chemotherapy correlates with longer PFS and OS in patients with HER2-positive mBC.

Keywords: metastatic breast cancer; inflammatory markers; trastuzumab; survival; platelet to lymphocyte ratio.

Introduction

The immune system plays a crucial and complex role in the progression of malignant neoplasms, often exhibiting a paradoxical influence on the process of carcinogenesis. On one hand, certain immune cells are adept at recognizing and eliminating tumor cells, thereby providing a protective effect for the patient. Conversely, other immune cells can facilitate the tumor's ability to evade detection and suppression by the immune response (Heinrich & Korangy, 2022). Chronic low-grade inflammation has been identified as a significant factor in the proliferation and survival of cancer cells. This persistent inflammatory state fosters the development of an immunosuppressive environment and disrupts the body's adaptive immune responses. As a result, the risk of recurrence and progression of malignant tumors is dramatically increased, highlighting the intricate relationship between the immune system and cancer development (McFarland et al., 2022).

The immune cells found in both peripheral blood and the tumor microenvironment play a crucial role in the development and progression of breast cancer (BC) (Nicolò et al., 2024). These immune cells, which include various types of lymphocytes, macrophages, and dendritic cells, can interact with tumor cells and influence the tumor's behavior (Faria et al., 2021). Specific immune cells present in the peripheral blood are responsible for producing chemokines. These signaling molecules facilitate communication between immune cells and promote neoangiogenesis – forming new blood vessels. This process is vital for tumors, providing them with nutrients and oxygen to sustain their growth. Furthermore, the chemokines produced by these immune cells can contribute to the metastatic spread of cancer, aiding in the dissemination of cancer cells from the primary tumor site to distant organs (Al Jarroudi et al., 2021).

The process of development and progression of breast cancer is inextricably linked with changes in indicators of systemic inflammation. Acute phase proteins (for example, C-reactive protein), inflammatory cytokines, neutrophils, platelets, lymphocytes, and monocytes are considered available and promising prognostic markers to assess the level of systemic inflammation (Smorodska et al., 2022). Based on simple parameters, it is possible to investigate combined indexes that more objectively reflect the condition of the immune system. They make it possible to exclude an isolated effect on certain laboratory parameters (for example, the effect of steroids on neutrophils). The most common indexes are the ratio of neutrophils and lymphocytes (NLR), platelets and lymphocytes (PLR), monocytes and lymphocytes (MLR), systemic immune inflammation index (SII), and pan-immune inflammatory value (PIV) (Chen et al., 2020). Inflammatory indexes are associated with the prognosis not only of BC but also of many other solid tumors. Many researchers consider them to be independent prognostic markers of progression-free survival (PFS) and overall survival (OS) (Passardi et al., 2023; Otsuka et al., 2023; Zhai et al., 2023).

The indisputable advantage of inflammation indexes is their non-invasiveness and availability, making this disease prediction method attractive. Understanding the direction and extent of the balance shift in the ratio of the number of neutrophils, platelets, monocytes, and lymphocytes allows a better assessment of the mechanism of carcinogenesis and finding potential ways to improve the results of treatment of metastatic breast cancer (mBC) (Cozzolino et al., 2021).

Breast cancer (BC) is a multifaceted disease characterized by a variety of subtypes, each exhibiting distinct behaviors and prognoses. Among these subtypes, HER2-positive metastatic breast cancer (mBC) is recognized as one of the most challenging and aggressive forms. The introduction of trastuzumab has considerably enhanced

the survival rates of patients with this subtype (Nolan et al., 2024). However, the effectiveness of this treatment can be influenced by different factors, highlighting the complexity of individual responses to therapy and the need for personalized treatment approaches (Pidubnyi et al., 2023; Vynnychenko & Moskalenko 2024).

Our study aimed to identify independent predictors of the efficacy of trastuzumab therapy affecting PFS and OS in patients with HER2-positive mBC.

Materials and methods

Research design and bioethics approval. 78 HER2-positive mBC patients treated with trastuzumab at the Sumy Regional Clinical Oncology Center from 2014 to 2024 were enrolled in a single-center retrospective study. Inclusion criteria were age ≥ 18 years, histologically and immunohistochemically confirmed diagnosis of HER2-positive BC (3+ or 2+ and FISH-positive), metastatic stage of the disease, trastuzumab-containing regimen (trastuzumab monotherapy or trastuzumab plus chemotherapy, at least two cycles), the available results of a complete blood count test before starting trastuzumab therapy. Exclusion criteria were unknown BC subtype or HER2 status, early BC, treatment regimen without trastuzumab, history of other malignancy, and inflammatory, autoimmune, and infectious diseases within two weeks before starting systemic treatment. The follow-up period continued for at least 18 months. The study was conducted following the Declaration of Helsinki and was approved by the Local Ethics Committee of the Sumy Regional Clinical Oncology Center (protocol 2/2, dated January 15, 2024). All alive patients signed informed consent forms.

Assessment of response to treatment and follow-up period. Response to treatment was assessed every 2-3 cycles according to local practice. The Response Evaluation Criteria in Solid Tumors (Recist 1.1) were used to evaluate the results. The objective response rate (ORR) was considered as the total number of patients with complete response (CR) (complete disappearance of tumor and metastases) and partial response (PR) (decrease of tumor burden by $\geq 30\%$). The disease control rate (DCR) was calculated as the total number of patients with CR, PR, and stable disease (SD) (decrease of tumor burden by $<30\%$ or increase $>20\%$). PFS was defined as the time between initiation of trastuzumab therapy and disease progression (PD). The appearance of new metastatic lesions or an increase in the already existing tumor burden by 20% or more was considered disease progression. OS was defined as the time from initiation of trastuzumab therapy to patient death from any cause. Telephone contacts were conducted every three months to assess the survival status. In the case of losing contact with the patient and his relatives, information about the date of death was obtained from the National Cancer Register of the Sumy Regional Clinical Oncology Center. The follow-up period continued until the patient's death or the database lock (1 July 2024).

Collection of information and its evaluation. All data about the clinicopathological characteristics of patients (age, number of metastases, menopausal status, hormonal status) were collected in the primary medical documentation. Complete blood count test results were evaluated up to one week before the start of trastuzumab therapy. MLR was defined as the ratio of the number of monocytes to lymphocytes, NLR – as the ratio of neutrophils to lymphocytes, PLR – as the ratio of platelets to lymphocytes, PIV – as the ratio of the product of neutrophils, platelets, and monocytes to lymphocytes.

Statistical analysis. All calculations were performed in the Stata V.18.0 software environment (StataCorp, Texas, USA; www.stata.com; 2024). The results were considered statistically significant at a P value of ≤ 0.05 . Cut-off values of inflammatory markers and area under the curves (AUC) were determined by ROC analysis. AUC ≥ 0.7 was considered statistically significant. Factors affecting PFS and OS were determined using the multivariate Cox proportional hazard model. The following clinicopathological characteristics were evaluated as prognostic factors: age (≥ 55 vs. <55), number of metastases (<3 vs. ≥ 3), menopausal status (premenopausal vs. postmenopausal), hormonal status (positive vs. negative), trastuzumab-containing regi-

men (trastuzumab monotherapy versus trastuzumab plus chemotherapy).

Results

Characteristics of patients. Seventy-eight HER2-positive mBC patients were enrolled in the retrospective study. The median age of the patients was 55 years (range 27–77). Sixty-six (84.6%) patients had less than three metastatic sites. Twenty-four (30.8%) patients had a premenopausal status, and 46 (59.0%) had a positive hormonal status. Twenty-seven (34.6%) patients received trastuzumab monotherapy.

PLR was the most sensitive and specific peripheral blood marker (AUC = 0.762, 95% confidence interval (CI) 0.646–0.847). PIV (AUC = 0.654, 95% CI 0.538–0.758), MLR (AUC = 0.641, 95% CI 0.524–0.747) and NLR (AUC = 0.581, 95% CI 0.459–0.688) were less sensitive (Fig. 1). The NLR, PLR, MLR, and PIV cut-off values were 2.62, 153.8, 0.22, and 155.4, respectively. Table 1 summarizes the basic clinicopathological characteristics of the patients.

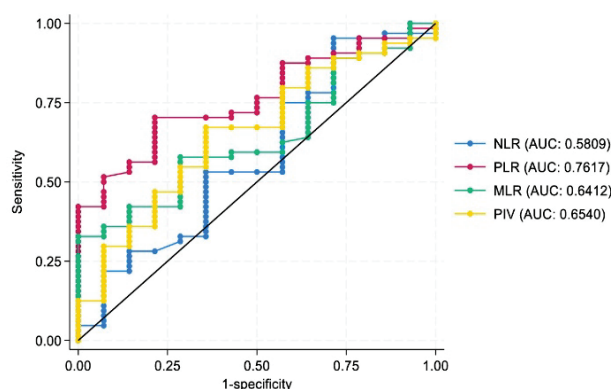


Fig. 1. ROC curves for evaluating NLR, PLR, MLR, and PIV as predictors of trastuzumab resistance

Table 1
Baseline clinicopathological characteristics of patients

Clinicopathological characteristics	Total number of patients (%), n = 78
Age (years), n (%)	
Median	55
Range	27–77
<55	33 (42.3)
≥ 55	45 (57.7)
The number of metastases	
<3	66 (84.6)
≥ 3	12 (15.4)
Menopausal status, n (%)	
Premenopausal	24 (30.8)
Postmenopausal	54 (69.2)
Hormonal status, n (%)	
Positive	46 (59.0)
Negative	32 (41.0)
Trastuzumab-containing regimen:	
Trastuzumab monotherapy	27 (34.6)
Trastuzumab+chemotherapy	51 (65.4)
NLR	
≤ 2.62 (low)	38 (48.7)
>2.62 (high)	40 (51.3)
PLR	
≤ 153.8 (low)	26 (33.3)
>153.8 (high)	52 (66.7)
MLR	
≤ 0.22 (low)	35 (44.9)
>0.22 (high)	43 (55.1)
PIV	
≤ 155.4 (low)	30 (38.5)
>155.4 (high)	48 (61.5)

The impact of inflammatory markers and basic clinicopathological characteristics patients on PFS. We compared the results of PFS according to the investigated markers of inflammation. Significantly better PFS was established in patients with low NLR (Log-rank $P = 0.0054$), low PLR (Log-rank $P = 0.0011$), low MLR (Log-rank $P = 0.0363$), and low PIV (Log-rank $P = 0.0018$). Median PFS in patients with low NLR was 15.5 months versus 9.3 months in patients with

high NLR. The median PFS for low PLR was 23.0 months versus 12.4 months for high PLR. The median PFS for low MLR was 16.2 months versus 11.1 months for high MLR. The median PFS for low PIV was 16.2 months versus 9.7 months for high PIV. Therefore, each of the investigated markers of inflammation had a statistically significant impact on PFS (Fig. 2).

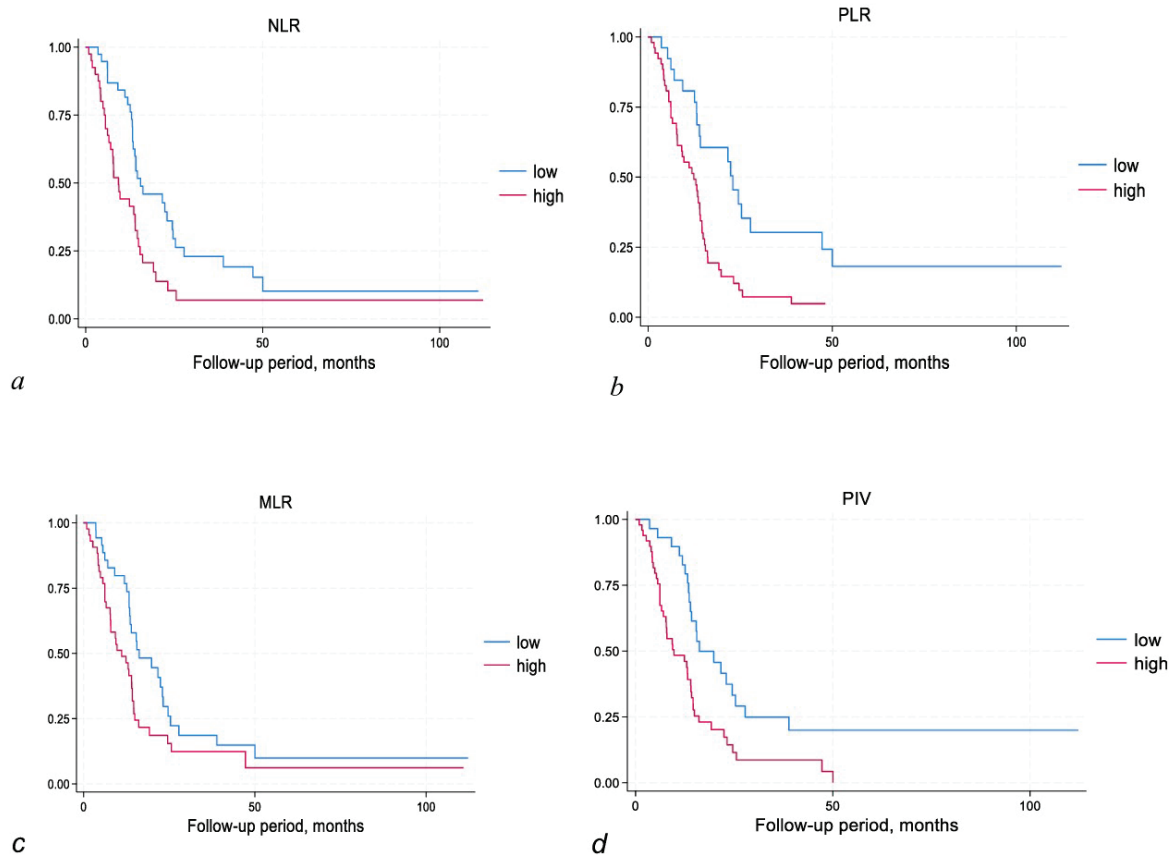


Fig. 2. Kaplan-Meier curves showing PFS according to NLR (a), PLR (b), MLR (c), and PIV (d) baseline levels

Multivariate analysis assessed the prognostic impact of age, number of metastases, menopausal status, hormonal status, trastuzumab-containing regimen, and inflammatory indexes on PFS in HER2-positive mBC patients treated with trastuzumab. Trastuzumab-containing regimen ($P = 0.0001$) and PLR ($P = 0.0040$) were independent predictors of the PFS. Patients who received chemotherapy plus trastuzumab and whose PLR before treatment was low had significantly better PFS (Table 2).

Table 2
Multivariate Cox proportional hazard model for assessing the impact of clinicopathological characteristics on PFS

Clinicopathological characteristics	Hazard ratio	95% CI	P value
Age (<55 versus ≥ 55)	1.28	0.53–3.06	0.578
The number of metastases (<3 versus ≥ 3)	0.91	0.43–1.95	0.827
Menopausal status (premenopausal versus postmenopausal)	1.11	0.43–2.84	0.814
Hormonal status (positive versus negative)	1.69	0.99–2.88	0.053
Trastuzumab-containing regimen (Trastuzumab monotherapy versus Trastuzumab+chemotherapy)	0.22	0.12–0.41	<0.001
NLR (low versus high)	0.95	0.49–1.82	0.886
PLR (low versus high)	2.99	1.43–6.26	0.004
MLR (low versus high)	1.11	0.57–2.18	0.742
PIV (low versus high)	1.91	0.98–3.75	0.057

The impact of inflammatory markers and clinicopathological characteristics on OS. Inflammatory markers were correlated with OS in the same way as with PFS. Patients with low NLR (Log-rank $P = 0.0006$), low PLR (Log-rank $P = 0.0002$), low MLR (Log-rank $P = 0.0023$), and low PIV (Log-rank $P = 0.0017$) had significantly

better OS. The median OS in patients with low NLR was 37.9 versus 23.0 months in patients with high NLR. The median OS for low PLR was 80.4 versus 25.1 months for high PLR. The median OS for low MLR was 40.3 versus 25.3 months for high MLR. The median OS for low PIV was 42.1 versus 25.3 months for high PIV. Therefore, each studied inflammation index had a statistically significant impact on the OS (Fig. 3).

Multivariate analysis evaluated the prognostic impact of age, number of metastases, menopausal status, hormonal status, trastuzumab-containing regimen, and inflammatory indexes on OS in HER2-positive mBC patients treated with trastuzumab. Trastuzumab-containing regimen ($P = 0.0001$) and PLR ($P = 0.029$) were independent predictors of the effectiveness of trastuzumab therapy, which impacts OS (Table 3).

Table 3
Multivariate Cox proportional hazard model for assessing the impact of clinicopathological characteristics on OS

Clinicopathological characteristics	HR	95% CI	P value
Age (<55 versus ≥ 55)	0.94	0.3–2.57	0.905
The number of metastases (<3 versus ≥ 3)	2.19	0.98–4.92	0.056
Menopausal status (premenopausal versus postmenopausal)	1.43	0.44–4.57	0.544
Hormonal status (positive versus negative)	1.28	0.68–2.43	0.437
Trastuzumab-containing regimen (Trastuzumab monotherapy versus Trastuzumab+chemotherapy)	0.30	0.15–0.58	<0.001
NLR (low versus high)	2.15	0.99–4.67	0.052
PLR (low versus high)	2.70	1.10–6.62	0.029
MLR (low versus high)	0.82	0.30–2.20	0.696
PIV (low versus high)	2.02	0.72–5.67	0.177

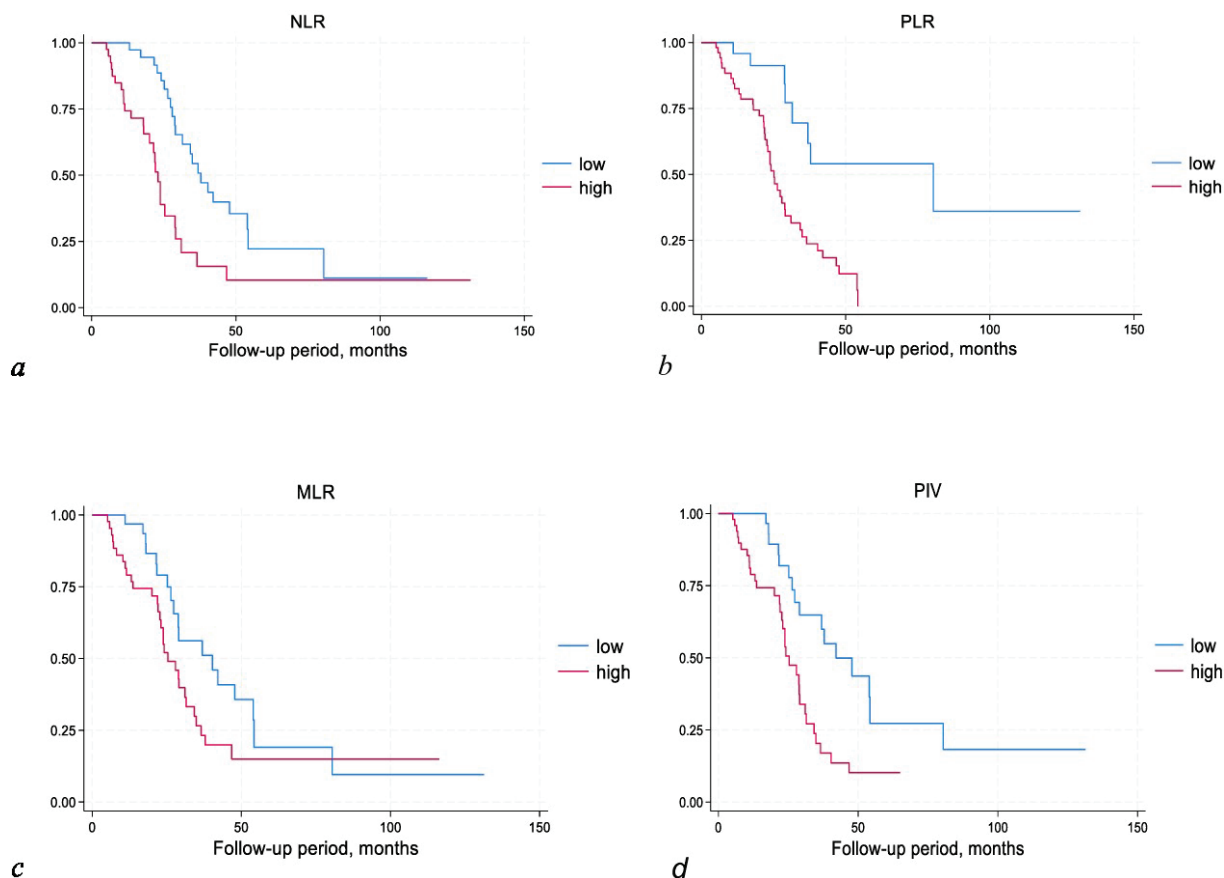


Fig. 3. Kaplan-Meier curves showing OS according to NLR (a), PLR (b), MLR (c), and PIV (d) baseline levels

Correlation of inflammatory markers with objective response rate (ORR) and disease control rate (DCR). The median follow-up period was 29 months (range 5–131). At the time of database lock, 64 (82.1%) patients had disease progression, and 48 (61.5%) had died due to disease progression or some other cause. The CR, PR, SD, and PD were registered in 3 (3.8%), 45 (57.7%), 22 (28.2%), and 8 (10.3%) respectively. ORR for the investigated cohort was 61.5%, and DCR – 89.7%. We additionally assessed the DCR for established independent predictors of the efficacy of trastuzumab therapy. Therefore, for patients with low PLR, DCR was 100.0% versus 84.6% for high PLR ($P = <0.0001$). DCR was 81.4% in patients treated with trastuzumab monotherapy versus 94.1% in those treated with trastuzumab plus chemotherapy ($P = 0.0485$).

Discussion

We showed that PLR and trastuzumab-containing regimens are independent predictors of trastuzumab efficacy in HER2-positive mBC patients. They have a significant impact on prognosis and survival. High PLR is associated with a lower PFS. Such patients demonstrate worse DCR than those whose PLR is low. This marker is available in routine practice and may help define the category of patients who may benefit from trastuzumab.

Platelets play an important role in the development and metastasis of BC. These peripheral blood cells stimulate T-helper cell differentiation and modulate adaptive immune responses (Stoiber, & Asinger, 2020). Platelets can impact on the innate immunity and change the differentiation of monocytes. In addition, they contribute to the formation of blood clots and trigger the lysophosphate-dependent mechanism of metastasis (Laface et al., 2024).

Platelet endothelial cell growth factor and transforming growth factor beta contribute to transmitting proliferative signals. Potential mediators in this process are extracellular vesicles. The combined effect of all factors increases cell proliferation and aggressiveness of BC (Zuo et al., 2019). Platelets significantly influence the progression of the disease. Cross-linking ligands of plasma proteins and adhesion

proteins contribute to the attachment of platelets to the vessel wall. After that, tumor cells are fixed to them and avoid apoptosis. In addition, tumors can increase the production of aberrant surface proteins and stimulate interaction with platelets. After anchoring on the wall of microvessels, the process of extravasation and metastasis development begins (Tang et al., 2023).

The invasive ability of BC is enhanced by high levels of interleukin-8. Their enhanced synthesis results from an increase in the number of platelets and activation of the AKT signaling pathway. Interestingly, aspirin can reduce the level of interleukin-8 and the invasive potential of the tumor (Johnson et al., 2019).

Lymphocytes, unlike platelets, are considered the primary effector cells responsible for antitumor immunity (Xie et al., 2020). They inhibit migration and proliferation and stimulate the cytotoxic death of cancer cells (Ogiya et al., 2016). All the above explains the negative impact of high PLR on PFS and OS.

The correlation between inflammatory markers and the effectiveness of therapy and survival in patients with HER2-positive mBC is widely covered in the scientific literature. Ligorio et al. (2021) investigated the prognostic impact of inflammatory markers on the effectiveness of taxane therapy, trastuzumab, and pertuzumab. High baseline PLR, MLR, and PIV were the prognostic factors for PFS, while high MLR and PIV predicted poor prognosis and low OS. Ding et al. (2020) found a strong correlation between lower NLR and longer PFS in patients treated with trastuzumab. Imamura et al. (2019) confirmed the negative impact of high PLR and NLR on the efficacy of trastuzumab emtansine therapy for second-line therapy of HER2-positive mBC. The results of our study are similar to those obtained by Blanchette et al. (2018). Baseline low PLR was confirmed as an independent predictor of better survival and effective trastuzumab therapy.

We found that a high baseline PLR was associated with a lower DCR in HER2-positive mBC patients. However, other factors can impact the effectiveness of treatment. Our study demonstrated that, in addition to PLR, the trastuzumab-containing regimen is an independent predictor of survival. Patients using trastuzumab plus chemother-

rapy had significantly better PFS and OS compared to those treated with trastuzumab alone.

The therapeutic effect of trastuzumab consists in stimulating the immune response. Specific monoclonal antibodies attach to cell membranes and induce cell death. Natural killer cells have Fc γ receptors, which contact the Fc region of trastuzumab. This interaction results in the release of cytotoxic substances and the death of target cells. Thus, an inflammatory tumor environment is developed and stimulates the appearance of tumor-specific T cells. In general, trastuzumab has a “vaccine effect” and could be potentially effective as monotherapy in patients with HER2-positive mBC. Vogel et al. (2023) evaluated the efficacy and safety of trastuzumab as a first-line monotherapy in 114 patients with mBC. The ORR was 26%. Trastuzumab has demonstrated a high safety profile. The authors concluded that this targeted drug can be used as a single agent for the treatment of HER2-positive mBC.

Isogai et al. (2023), in their case report, demonstrated the experience of a complete pathological response to a single dose of trastuzumab in an 88-year-old female. Ji et al. (2023) used trastuzumab monotherapy in a male patient with accessory breast cancer. The authors concluded that trastuzumab monotherapy can be successfully used in certain categories of patients, especially if there are chemotherapy-related contraindications.

Several studies have compared the efficacy of trastuzumab monotherapy and the combination of chemotherapy and trastuzumab. The advantages of combined treatment were first reported by Slamon et al. (2001). The authors demonstrated that trastuzumab combined with chemotherapy was associated with higher ORR, longer time to disease progression, longer duration of response, lower 1-year mortality, and better OS. Modern research confirms these conclusions. Zhang et al. (2021) performed a meta-analysis of sixteen studies using trastuzumab to treat HER2-positive mBC patients. The taxane + trastuzumab + pertuzumab regimen showed the best efficacy and moderate safety. In the latest ASCO (American Society of Clinical Oncology) guidelines, this therapeutic regimen is considered the optimal treatment choice for first-line therapy. In cases when pertuzumab is unavailable, it is recommended that trastuzumab and chemotherapy be used (Al Sukhun et al., 2024).

The results of our study may be helpful in routine clinical practice for treating HER2-positive mBC patients and selecting the most suitable candidates for targeted therapy with trastuzumab. The main limitations of this study are the retrospective design and the relatively small number of patients.

Conclusions

PLR and the trastuzumab-containing regimen have prognostic value for evaluating the efficacy of trastuzumab therapy and the prognosis of HER2-positive mBC. Low PLR is associated with better PFS, OS, and high DCR. PLR may be an effective marker for identifying the candidates most benefit from trastuzumab. Compared with trastuzumab monotherapy, the combination of trastuzumab and chemotherapy correlates with longer PFS and OS in HER2-positive mBC patients.

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The authors declare no conflict of interest.

References

Al Jarroudi, O., El Bairi, K., Abda, N., Zaimi, A., Jaouani, L., Chibani, H., & Afqir, S. (2021). Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of outcomes in inflammatory breast cancer. *Biomarkers in Medicine*, 15(14), 1289–1298.

Al Sukhun, S., Temin, S., Barrios, C. H., Antone, N. Z., Guerra, Y. C., Chavez-MacGregor, M., Chopra, R., Danso, M. A., Gomez, H. L., Homian, N. M.,

Kandil, A., Kithaka, B., Koczwara, B., Moy, B., Nakigudde, G., Petracci, F. E., Rugo, H. S., El Saghir, N. S., & Arun, B. K. (2024). Systemic treatment of patients with metastatic breast cancer: ASCO resource-stratified guideline. *JCO Global Oncology*, 10, e2300285.

Blanchette, P. S., Desautels, D. N., Pond, G. R., Bartlett, J. M. S., Nofech-Mozes, S., Yaffe, M. J., & Pritchard, K. I. (2018). Factors influencing survival among patients with HER2-positive metastatic breast cancer treated with trastuzumab. *Breast Cancer Research and Treatment*, 170(1), 169–177.

Chen, L., Kong, X., Yan, C., Fang, Y., & Wang, J. (2020). The research progress on the prognostic value of the common hematological parameters in peripheral venous blood in breast cancer. *Oncotargets and Therapy*, 13, 1397–1412.

Cozzolino, M., Cocco, S., Piezzo, M., Celia, G., Costantini, S., Abate, V., Capone, F., Barberio, D., Girelli, L., Cavicchiolo, E., Ascierto, P. A., Madonna, G., Budillon, A., & De Laurentiis, M. (2021). A psychosocial genomics pilot study in oncology for verifying clinical, inflammatory and psychological effects of mind-body transformations-therapy (MBT-T) in breast cancer patients: Preliminary results. *Journal of Clinical Medicine*, 10(1), 136.

Ding, N., Huang, J., Li, N., Yuan, J., Wang, S., & Xiao, Z. (2020). Roles of neutrophil/lymphocyte ratio in prognosis and in differentiation of potential beneficiaries in HER2-positive breast cancer with trastuzumab therapy. *BMC Cancer*, 20(1), 235.

Faria, S. S., Costantini, S., de Lima, V. C. C., de Andrade, V. P., Rialland, M., Cedric, R., Budillon, A., & Magalhães, K. G. (2021). NLRP3 inflammasome-mediated cytokine production and pyroptosis cell death in breast cancer. *Journal of Biomedical Science*, 28(1), 26.

Heinrich, B., & Korangy, F. (2022). Plasticity of innate lymphoid cells in cancer. *Frontiers in Immunology*, 13, 886520.

Imamura, M., Morimoto, T., Egawa, C., Fukui, R., Bun, A., Ozawa, H., Miyagawa, Y., Fujimoto, Y., Higuchi, T., & Miyoshi, Y. (2019). Significance of baseline neutrophil-to-lymphocyte ratio for progression-free survival of patients with HER2-positive breast cancer treated with trastuzumab emtansine. *Scientific Reports*, 9(1), 1811.

Isogai, A., Kotani, H., Sawaki, M., Hattori, M., Yoshimura, A., Kataoka, A., Nozawa, K., Ozaki, Y., Endo, Y., Nakakami, A., Komaki, R., & Iwata, H. (2023). Single-dose trastuzumab monotherapy achieved pathological complete response (pCR) in a patient with HER2-positive breast cancer: A case report. *Surgical Case Reports*, 9(1), 112.

Ji, W., & Guo, W. (2023). Male accessory breast cancer successfully treated with single-agent Trastuzumab: A case report. *American Journal of Men's Health*, 17(3), 15579883231171010.

Johnson, K. E., Ceglowski, J. R., Roweth, H. G., Forward, J. A., Tippy, M. D., El-Husayni, S., Kulenthirarajan, R., Malloy, M. W., Machlus, K. R., Chen, W. Y., Italiano Jr, J. E., & Battinelli, E. M. (2019). Aspirin inhibits platelets from reprogramming breast tumor cells and promoting metastasis. *Blood Advances*, 3(2), 198–211.

Laface, C., Ricci, A. D., Vallarelli, S., Ostuni, C., Rizzo, A., Ambrogio, F., Centonze, M., Schirizzi, A., De Leonadis, G., D'Alessandro, R., Lotesoriere, C., & Giannelli, G. (2024). Autotaxin-Lysophosphatidate axis: Promoter of cancer development and possible therapeutic implications. *International Journal of Molecular Sciences*, 25(14), 7737.

Ligorio, F., Cucà, G., Zattarin, E., Lobefaro, R., Zambelli, L., Leporati, R., Rea, C., Mariani, G., Bianchi, G. V., Capri, G., de Braud, F., & Vermieri, C. (2021). The pan-immune-inflammation-value predicts the survival of patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer treated with first-line Taxane-Trastuzumab-Pertuzumab. *Cancers*, 13(8), 1964.

Mandó, P., Rivero, S. G., Rizzo, M. M., Pinkasz, M., Levy, E. M. (2021). Targeting ADCC: A different approach to HER2 breast cancer in the immunotherapy era. *Breast*, 60, 15–25.

McFarland, D. C., Doherty, M., Atkinson, T. M., O'Hanlon, R., Breitbart, W., Nelson, C. J., & Miller, A. H. (2022). Cancer-related inflammation and depressive symptoms: Systematic review and meta-analysis. *Cancer*, 128(13), 2504–2519.

Nicolò, E., Gianni, C., Pontolillo, L., Serafini, M. S., Munoz-Arcos, L. S., Andreopoulou, E., Curigliano, G., Reduzzi, C., & Cristofanilli, M. (2024). Circulating tumor cells et al.: Towards a comprehensive liquid biopsy approach in breast cancer. *Translational Breast Cancer Research*, 5, 10.

Nolan, L., Davey, M. G., Calpin, G. G., Ryan, É. J., & Boland, M. R. (2024). Risk of locoregional recurrence after breast cancer surgery by molecular subtype – a systematic review and network meta-analysis. *Irish Journal of Medical Science*, 2024, in press.

Ogiya, R., Niikura, N., Kumaki, N., Bianchini, G., Kitano, S., Iwamoto, T., Hayashi, N., Yokoyama, K., Oshitani, R., Terao, M., Morioka, T., Tsuda, B., Okamura, T., Saito, Y., Suzuki, Y., & Tokuda, Y. (2016). Comparison of tumor-infiltrating lymphocytes between primary and metastatic tumors in breast cancer patients. *Cancer Science*, 107(12), 1730–1735.

- Otsuka, R., Hayashi, H., Uesato, M., Hayano, K., Murakami, K., Toyozumi, T., Matsumoto, Y., Kurata, Y., Nakano, A., Takahashi, Y., Arasawa, T., & Matsubara, H. (2023). Inflammatory and nutritional indices as prognostic markers in elderly patients with gastric cancer. *Anticancer Research*, 43(11), 5261–5267.
- Passardi, A., Azzali, I., Bittoni, A., Marisi, G., Rebuzzi, F., Molinari, C., Bartolini, G., Matteucci, L., Sullo, F. G., Debonis, S. A., Gallio, C., Monti, M., Valgiusti, M., Muratore, M., Rapposelli, I. G., Ulivi, P., & Frassinetti, G. L. (2023). Inflammatory indices as prognostic markers in metastatic colorectal cancer patients treated with chemotherapy plus Bevacizumab. *Therapeutic Advances in Medical Oncology*, 15, 1–13.
- Piddubnyi, A., Kolomiiets, O., Danilchenko, S., Stepanenko, A., Moskalenko, Y., & Moskalenko, R. (2023). The prospects of using structural phase analysis of microcalcifications in breast cancer diagnostics. *Diagnostics*, 13(4), 737.
- Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., Fleming, T., Eiermann, W., Wolter, J., Pegram, M., Baselga, J., & Norton, L. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England Journal of Medicine*, 344(11), 783–792.
- Smorodska, O., Moskalenko, Y., Kononenko, M., & Ivanov, S. (2022). Inflammation indexes as predictors of disease recurrence in patients with surgically resected non-small cell lung cancer. *Eastern Ukrainian Medical Journal*, 10(4), 379–388.
- Stoiber, D., & Assinger, A. (2020). Platelet-leukocyte interplay in cancer development and progression. *Cells*, 9(4), 855.
- Tang, Y., Qian, C., Zhou, Y., Yu, C., Song, M., Zhang, T., Min, X., Wang, A., Zhao, Y., & Lu, Y. (2023). Activated platelets facilitate hematogenous metastasis of breast cancer by modulating the PDGFR- β /COX-2 axis. *iScience*, 26(9), 107704.
- Vogel, C. L., Cobleigh, M. A., Tripathy, D., Gutheil, J. C., Harris, L. N., Fehrenbacher, L., Slamon, D. J., Murphy, M., Novotny, W. F., Burchmore, M., Shak, S., Stewart, S. J., & Press, M. (2023). Efficacy and safety of Trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *Journal of Clinical Oncology*, 41(9), 1638–1645.
- Vynnychenko, O. I., & Moskalenko, Y. V. (2024). Prognostic impact of body mass index on metastatic HER2-positive breast cancer survival. *Ukrainian Journal of Radiology and Oncology*, 32(3), 363–376.
- Xie, L., Fang, J., Yu, J., Zhang, W., He, Z., Ye, L., Wang, H. (2023). The role of CD4+ T cells in tumor and chronic viral immune responses. *MedComm*, 4(5), e390.
- Zhai, W. Y., Duan, F. F., Lin, Y. B., Lin, Y. B., Zhao, Z. R., Wang, J. Y., Rao, B. Y., Zheng, L., & Long, H. (2023). Pan-immune-inflammatory value in patients with non-small-cell lung cancer undergoing neoadjuvant immunotherapy. *Journal of Inflammation Research*, 16, 3329–3339.
- Zhang, X., Leng, J., Zhou, Y., Mao, F., Lin, Y., Shen, S., & Sun, Q. (2021). Efficacy and safety of anti-HER2 agents in combination with chemotherapy for metastatic HER2-positive breast cancer patient: A network meta-analysis. *Frontiers in Oncology*, 11, 731210.
- Zuo, X. X., Yang, Y., Zhang, Y., Zhang, Z. G., Wang, X. F., & Shi, Y. G. (2019). Platelets promote breast cancer cell MCF-7 metastasis by direct interaction: Surface integrin $\alpha 2\beta 1$ -contacting-mediated activation of Wnt- β -catenin pathway. *Cell Communication and Signaling*, 17(1), 142.