Article published online: 2025-10-30

THIEME OPEN ACCESS

Original Article

Pan-Immune-Inflammation Value: A Novel Marker for Chemotherapy Response in Locally Advanced Breast Cancer

K. N. Lokesh[1] Guruprasad C. Shenoy[1] Manjunath S. Hiremani[1] Rudresha A. H.[1] L K. Rajeev[1] Smitha C. Saldanha[1] G. V. Giri[2] Suresh Babu M. C.[1]

[1] Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
[2] Department of Medicine, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

Address for correspondence Guruprasad C. Shenoy, MD, Senior Resident, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka 560029, India (e-mail: guruprasadshenoy11@gmail.com).

Ind J Med Paediatr Oncol

Abstract

Introduction Neoadjuvant chemotherapy (NACT) is the cornerstone in the management of locally advanced breast cancer (LABC), aiming to reduce tumor burden and achieve pathological complete response (pCR), which correlates with improved survival outcomes. Pan-immune-inflammation value (PIV), calculated from peripheral blood counts, reflects systemic inflammation and immune status and has been proposed as prognostic and predictive biomarker in solid tumors.

Objective This article evaluates the role of PIV as a predictor marker of response to NACT in locally advanced breast carcinoma and to study the pathological response (residual cancer burden [RCB] score) after NACT in relation to PIV.

Materials and Methods The current prospective observational investigation was conducted at a tertiary cancer center in Bangalore and included 168 patients with biopsy-proven LABC treated between January 2023 and December 2024. PIV was calculated as (neutrophils × monocytes × platelets)/lymphocytes from pretreatment complete blood counts. All patients received standard anthracycline-taxane–based NACT, with HER2-positive patients receiving trastuzumab. Pathological response was evaluated by employing RCB scoring system. Statistical analysis was done by employing SPSS v30.

Results Among the 168 patients, insignificant associations were observed between PIV status and demographic or baseline clinical characteristics. However, PIV was significantly associated with pathological response. Of the 36 patients who achieved pCR (RCB 0), 88.9% had low PIV and only 11.1% had high PIV ($p < 0.001$). In contrast, among the 132 nonresponders (RCB 1–3), 78.8% had high PIV. Receiver operating characteristic analysis identified a PIV cutoff of 543.51 with area under the curve of 0.877. This threshold provided sensitivity of 78.8% and a specificity of 88.9% for predicting pCR. Analysis of variance confirmed statistically significant difference in mean PIV between responders and nonresponders ($p < 0.001$).

Conclusion PIV is a promising, accessible biomarker for predicting response to NACT in LABC. Its use in pretreatment stratification may inform therapeutic decision-making and optimize individualized treatment strategies.

Keywords
- locally advanced breast cancer
- pan-immune-inflammation value
- chemotherapy
- residual cancer burden score

DOI https://doi.org/10.1055/s-0045-1812853.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Breast cancer is the most common malignancy in women[1,2] exhibiting the highest prevalence among all malignancies that affect women, as cited by the World Health Organization.[3]

Standard of care for patients having locally advanced breast cancer (LABC) is neoadjuvant chemotherapy (NACT), which involves the administration of chemotherapy prior to local treatment (surgery).[4] Furthermore, the downstaging of primary tumor among patients having earlier phases of breast cancer may facilitate breast-conserving therapy and offer opportunity to downstage the axilla, thereby eliminating the necessity for axillary treatment in certain patients.

The relationship between chronic inflammation and cancer has gained significant popularity in the past two decades, and the diagnostic and therapeutic value of inflammatory markers has been comprehensively investigated.

Prognostic value of peripheral blood-derived inflammation markers, including the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio, and platelet-lymphocyte ratio, in numerous malignancies involving solid organ has been demonstrated, on basis of assumption that peripheral blood cell populations can present information regarding intratumoral immune system status.[5–7] These markers were reported for predicting NACT response in breast cancer, in addition to their prognostic value.[8–10]

In 2020, Fucà et al reported that a novel systemic immune score, pan-immune-inflammation value (PIV), was more effective in identifying survival outcomes than other immune-inflammatory biomarkers, such as NLR, in advanced colorectal cancer patients.[11] Nevertheless, there is lack of investigation on predictive and prognostic value of PIV among breast cancer patients receiving NACT. Therefore, our objective was to investigate the PIV as predictive marker of response to NACT in LABC.

Materials and Methods

This was a prospective research conducted on patients attending a tertiary cancer care center in Bangalore. After obtaining written informed consent from the participants, patients undergoing treatment from January 2023 to December 2024 were enrolled into the study. Patients having LABC who fulfilled the inclusion criteria were recruited.

Inclusion Criteria

1. Age $>$ 18 years
2. Biopsy-proven breast cancer
3. LABC
   (a) Estrogen receptor, progesterone receptor positive, Her2neu negative
   (b) Triple-negative breast carcinoma (TNBC)
   (c) Her 2neu positive patients treated with trastuzumab-based regimen

Exclusion Criteria

1. Patient not willing to give informed consent
2. Metastatic breast carcinoma
3. Diagnosis of ductal carcinoma in situ
4. Recurrent breast carcinoma

The study cohort included patients with inflammatory breast cancer, with no cases of active infection, autoimmune disease, human immunodeficiency virus infection, or pregnancy present. The study collected comprehensive clinicopathologic data, including age, menstrual status, histologic type, clinical stage before initiation of NACT, histologic grade, chemotherapy regimen, and molecular biomarker status (ER, PR, HER2, and Ki-67). A complete blood count was obtained prior to treatment (baseline), and the absolute counts of neutrophils, monocytes, platelets, and lymphocytes were recorded. The PIV was evaluated by multiplying neutrophil count (10^3/μL) by platelet count (10^3/μL) and monocyte count (10^3/μL), and dividing product by lymphocyte count (10^3/μL). All patients were provided NACT using anthracyclines followed by taxanes. Those patients who had HER2+ cancer received trastuzumab as one of their treatments. After surgery, tissue was examined, and residual cancer burden (RCB) score was calculated.[12]

Primary and Secondary Outcomes

Primary outcome:

1. Correlation between PIV and pathological complete response (pCR) post-NACT.

Secondary outcomes:

2. Association of PIV with other clinical and pathological variables, viz., demographic and comorbidity profile, tumor stage and subtype, histology, ductal carcinoma in situ (DCIS)/lobular carcinoma in situ (LCIS) status, RCB classification, and Ki 67 index.

Statistical Analysis

Statistical analysis was done by employing SPSS (Statistical Package for the Social Sciences), version 30. After entering data into Microsoft Excel, it was imported into SPSS for further analysis. Descriptive statistics were evaluated for all variables that were analyzed. Quantitative variables were evaluated by employing mean or median values, and standard deviation or interquartile range. When dealing with qualitative variables, frequencies and proportions were determined.

Categorical variables were determined for associations by performing a chi-square test. Area under the receiver operating characteristic (ROC) curve was calculated for estimating optimum cutoff values for PIV, sensitivity, as well as specificity concerning breast cancer outcomes.

Ethical Approval

After obtaining clearance from the Institutional Ethics Committee (KMIO/MEC/2023/04/PG/MO/22) and written informed consent from the participants, patients undergoing treatment from January 2023 to December 2024 were enrolled into the

Table 1 Association of demographic and clinical parameters with PIV status in breast cancer patients

Variable	Category	High PIV (*n*, %)	Low PIV (*n*, %)	*p*-Value
Age	< 40 y	23 (63.9)	13 (36.1)	0.817
	40–60 y	64 (66.0)	33 (34.0)	
	> 60 y	21 (60.0)	14 (40.0)	
Type 2 DM	Yes	14 (66.7)	7 (33.3)	0.808
	No	94 (63.9)	53 (36.1)	
Hypertension	Yes	23 (74.2)	8 (25.8)	0.202
	No	85 (62.0)	52 (38.0)	
BMI (kg/m^2)	< 25	54 (69.2)	24 (30.8)	0.284
	25–30	41 (63.1)	24 (36.9)	
	> 30	13 (52.0)	12 (48.0)	
Parity	0	5 (55.6)	4 (44.4)	0.341
	1	18 (54.5)	15 (45.5)	
	2	65 (71.4)	26 (28.6)	
	3	19 (57.6)	14 (42.4)	
	4	1 (50.0)	1 (50.0)	
Menstrual status	Postmenopausal	66 (66.0)	34 (34.0)	0.574
	Premenopausal	42 (61.8)	26 (38.2)	

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PIV, pan-immune-inflammation value.

study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

A total of 168 patients were selected for the study. The association of age, comorbidities, body mass index (BMI), parity, and menstrual status with PIV status was analyzed. Statistically insignificant association between these parameters and PIV status were observed, as demonstrated in ►**Table 1**.

Statistically insignificant association between PIV status and tumor characteristics, including molecular subtype (HR+/HER2–, HER2+, TNBC), clinical stage, tumor size (T stage), or nodal status (N stage) was observed. However, an increasing trend in proportion of patients having high PIV was observed across advancing tumor stages. Specifically, patients suffering from stage IIIC disease, higher T stages (T4), and extensive nodal involvement (N3) exhibited a greater prevalence of high PIV. These outcomes are detailed in ►**Table 2**.

Insignificant associations were seen between PIV status and histologic subtype, presence of DCIS, LCIS, or Ki-67 proliferation index. Although high PIV appeared more frequently among patients experiencing invasive ductal carcinoma and elevated Ki-67 ($\geq$ 20%), these differences were statistically insignificant.

In contrast, RCB classification showed a highly significant correlation with PIV status. Patients who attained pCR (RCB 0) predominantly belonged to the low PIV group (88.9%), whereas high PIV was present in only 11.1% of these cases. Among nonresponders (RCB 1–3), high PIV was observed in 78.8% of patients, indicating a strong inverse association between PIV and chemotherapy response.

These findings underscore the potential role of PIV as predictive marker for pathological response to neoadjuvant treatment and are mentioned in ►**Table 3**.

ROC curve analysis was applied for evaluating diagnostic performance of PIV in predicting breast cancer. Area under the curve (AUC) was calculated to assess overall discriminatory ability.

A detailed analysis of ROC coordinates identified various cutoff points with corresponding sensitivity along with specificity values. Among these, optimal cutoff for PIV was determined to be 543.51, which yielded the highest Youden's index ($J = 0.677$) ►**Figure 1**. At this threshold, the sensitivity was 78.8% and the specificity was 88.9%, indicating a robust balance between true positive and true negative rates. Thus, a PIV value of 543.51 or higher was observed to be the most effective threshold for differentiating between patients with and without breast cancer in this cohort. AUC for PIV was 0.877, indicating excellent discriminatory ability.

One-way analysis of variance was employed for comparing mean PIV values between patients with and without pCR. The results demonstrated a statistically significant difference ($p < 0.001$).

Discussion

Our study encompassed patients aged 40 to 60 years (58%), with a smaller proportion aged below 40 (21.4%) or above 60

Table 2 Association of tumor characteristics (molecular subtype, clinical stage, T stage, and N stage) with PIV status

Variable	Category	High PIV (*n*, %)	Low PIV (*n*, %)	*p*-Value
Hormone status	HR+/HER2–	66 (68.8)	30 (31.2)	0.127
	HER2+	18 (50.0)	18 (50.0)	
	TNBC	24 (66.7)	12 (33.3)	
Clinical stage	Stage IIIA	44 (61.1)	28 (38.9)	0.334
	Stage IIIB	27 (60.0)	18 (40.0)	
	Stage IIIC	37 (72.5)	14 (27.5)	
T stage	T1	17 (60.7)	11 (39.3)	0.768
	T2	25 (61.0)	16 (39.0)	
	T3	23 (62.2)	14 (37.8)	
	T4a	21 (75.0)	7 (25.0)	
	T4b	22 (64.7)	12 (35.3)	
N stage	N0	28 (63.6)	16 (36.4)	0.226
	N1	28 (58.3)	20 (41.7)	
	N2	21 (58.3)	15 (41.7)	
	N3	31 (77.5)	9 (22.5)	

Abbreviations: PIV, pan-immune-inflammation value; TNBC, triple-negative breast carcinoma.

Table 3 Association of tumor microenvironment features and pathologic response markers (histological type, DCIS, LCIS, RCB class, and Ki-67) with PIV status

Variable	Category	High PIV (*n*, %)	Low PIV (*n*, %)	*p*-Value
Histology	Invasive ductal carcinoma (IDC)	97 (64)	55 (36)	0.695
	Other histology types	11 (68.8)	5 (31.2)	
DCIS	Present	30 (60.0)	20 (40.0)	0.450
	Absent	78 (66.1)	40 (33.9)	
LCIS	Present	36 (67.9)	17 (32.1)	0.504
	Absent	72 (62.6)	43 (37.4)	
RCB class	0 (pCR)	4 (11.1)	32 (88.9)	**< 0.001**
	1–3 (non-pCR)	104 (78.8)	28 (21.2)	
Ki-67	< 20%	11 (57.9)	8 (42.1)	0.537
	≥ 20%	97 (65.1)	52 (34.9)	

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; pCR, pathological complete response; PIV, pan-immune-inflammation value; RCB, residual cancer burden.

(20.6%). The distribution of high and low PIV was similar across age categories ($p = 0.817$). Similar observations were made in the studies by Şahin et al[13] and Lin et al,[14] where the median ages were 48 years, and insignificant difference in PIV stratification was found by age group. However, in the study by Demir et al,[15] which focused on a younger cohort (≤ 40 years), high PIV was paradoxically more common in younger patients ($p < 0.05$), possibly reflecting the inherently more aggressive tumor biology and inflammation profile in young-onset breast cancer.

Presence of comorbidities like type 2 diabetes mellitus and hypertension did not significantly distinguish between high and low PIV groups in our study ($p = 0.808$ and $p = 0.202$, respectively). In contrast, Lin et al[14] noted a slight increase in PIV among patients having higher BMI, though it was statistically insignificant. Our analysis across BMI categories (< 25, 25–30, > 30 kg/m^2) similarly showed no significant trend ($p = 0.284$), although proportion of patients having high PIV was lowest in the obese category (> 30 kg/m^2), which might warrant further exploration.

Parity and menstrual status also did not significantly associate with PIV status in our study ($p = 0.341$ and $p = 0.574$, respectively).

Analysis of tumor-related parameters revealed important trends. While molecular subtypes (HR+/HER2–, HER2+, and TNBC) did not indicate statistically significant associations with PIV ($p = 0.127$), we observed numerically higher proportions of high PIV among HR+/HER2– (68.8%) and TNBC (66.7%) patients. This aligns with Şahin et al,[13] who reported that ER as well as HER2 status were independent

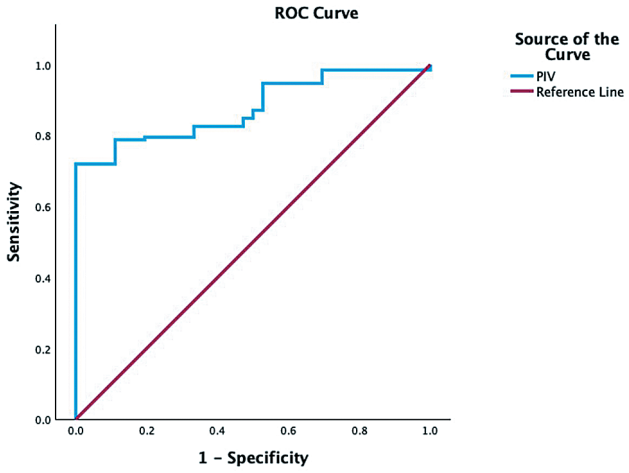

Fig. 1 Receiver operating characteristic (ROC) curve analysis of pan-immune-inflammation value (PIV) for predicting pathologic complete response (pCR) in breast cancer.

predictors of pCR and were associated with PIV on univariate analysis. Lin et al[14] demonstrated significant association between high PIV and ER negativity ($p = 0.02$), although PR and HER2 status were significantly insignificant. In Demir et al,[15] HR positivity was high overall (81.1%), and PIV stratification by molecular subtype was not reported.

Clinical stage analysis in our study showed a progressive increase in high PIV from stage IIIA (61.1%) to stage IIIC (72.5%) ($p = 0.334$), echoing the trend that greater tumor burden correlates with higher systemic inflammatory activation. Similarly, for T stage, the percentage of high PIV rose from 60.7% in T1 to 75.0% in T4a. Although these outcomes did not attain statistical significance, they demonstrate pattern observed by Şahin et al,[13] where higher T stage was significantly related to high PIV and lower pCR rates. In Lin et al,[14] T and N stages were independent predictors of overall survival (OS) and significantly correlated with PIV. Demir et al[15] observed significant associations between PIV and stage, especially advanced stages being more frequent in the high PIV group ($p < 0.05$).

With nodal status, a stepwise increase in high PIV was seen from N0 (63.6%) to N3 (77.5%) in our study, though statistically insignificant ($p = 0.226$). Lin et al[14] also reported a similar association, with N3 disease significantly more common in the high PIV group.

In cases when no tumor was noticed after pCR, a score of 0 was given based on the RCB system. Most individuals (89.9%) showing pCR belonged to the low PIV group, while few (11.1) were in the high PIV group ($p < 0.001$). Study found that the low PIV category applied to only 21.1% of cancer patients, while 78.8% were included in the high PIV group.

Histologic subtype (invasive ductal carcinoma vs. others) was not significantly related to PIV in our cohort ($p = 0.695$). This is similar to the investigation conducted by Lin et al,[14] where effect of histology on PIV was minimal. A patient's PIV determination was not affected by having DCIS or LCIS. Ki-67 is a reliable measure to evaluate cell growth, but difference between those with high and low PIV was insignificant ($p = 0.537$). Şahin et al[13] and Lin et al[14] found out that a high Ki-67 level is linked to pCR and results in a poorer survival rate.

PIV as a biomarker derives from its integration of key inflammatory mediators—neutrophils, monocytes, platelets, and lymphocytes—that significantly influence tumor biology and immune regulation. Neutrophils facilitate tumor progression and metastasis via angiogenesis, interleukin-1β signaling, and transforming growth factor-β-mediated epithelial-mesenchymal transition. Monocytes, as precursors to macrophages and myeloid-derived suppressor cells, support tumor invasion, angiogenesis, and immunosuppression. Platelets contribute by releasing angiogenic and inflammatory mediators, enabling metastatic dissemination and immune evasion. Conversely, lymphocytes predominantly mediate cytotoxic antitumor immunity. Thus, a low PIV signifies decreased tumor-promoting inflammation and enhanced lymphocyte-driven antitumor responses, correlating clinically with improved chemotherapy efficacy and patient survival.[16]

The findings align with those of Şahin et al,[13] who examined 743 patients with breast cancer who received NACT. They indicated that patients who have low PIV had greater chances of having a positive response to NACT and a multivariate analysis confirmed this finding (odds ratio: 3.32; 95% confidence interval: 1.53–7.21; $p = 0.002$). A PIV cutoff value of 306.4 was used, and results showed patients in the low PIV group had better chances of survival and freedom from disease, demonstrating prognostic and predictive value of the biomarker.

In our group, it was observed that PIV shows a very strong ability to predict pCR, with AUC of 0.877. Optimal cutoff value of 543.51, sensitivity of 78.8%, and specificity of 88.9%, mean PIV indicates if patients are less likely to have pCR after standard chemotherapy. Our diagnostic performance is much higher than 0.592, reported by Şahin et al. This could be because our patient selection was different, their PIV measures were not taken at same time, and stricter definition for pCR was employed in the current investigation.

Lin et al,[14] while focusing primarily on survival outcomes in operable breast cancer, also found that high PIV was significantly related to poorer OS (5-year OS: 62.5% in high PIV vs. 71.55% in low PIV; hazard ratio = 1.737; $p = 0.016$). Although they did not directly assess pCR, their findings support the broader negative prognostic implications of high PIV. Moreover, their multivariate analysis retained PIV as independent factor after adjusting for HER2 status, clinical stage, hormone receptor status, along with Ki-67 index.

By identifying patients with high PIV who are at elevated risk of chemoresistance, clinicians may be able to personalize therapeutic strategies, considering early integration of immunotherapy, alternative chemotherapy regimens, or enrollment in clinical trials targeting tumor inflammation and immune evasion. Conversely, patients with low PIV and higher likelihood of attaining pCR may potentially benefit from deescalated approaches, reducing treatment-related toxicity without compromising efficacy.

Conclusion

Our study underscores the potential of PIV as a simple, accessible biomarker for prediction of response to NACT in breast cancer. Although baseline characteristics did not differ significantly by PIV status, low PIV was strongly related to higher rates of pCR, suggesting better chemosensitivity. Considering its strong predictive performance, PIV may help in pretreatment risk stratification and guide treatment intensity, supporting its integration into clinical decision-making frameworks.

Authors' Contributions

i. Each author has made the following contributions toward the completion of the manuscript:

a. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.

b. Drafting the article or revising it critically for important intellectual content.

c. Final approval of the version to be published.

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Patient Consent

Informed consent was taken from each patient.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

The authors are indebted to the patients, their families, and staff involved in their care. Authors are also deeply grateful for all the help and support provided from the Department of Medical Oncology.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(01):7–30

2 Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet 2021;397(10286):1750–1769

3 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(03): 209–249

4 Yeo SK, Guan JL. Breast cancer: multiple subtypes within a tumor? Trends Cancer 2017;3(11):753–760

5 Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106(06): dju124

6 Gu L, Li H, Chen L, et al. Prognostic role of lymphocyte to monocyte ratio for patients with cancer: evidence from a systematic review and meta-analysis. Oncotarget 2016;7(22): 31926–31942

7 Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23 (07):1204–1212

8 Ni XJ, Zhang XL, Ou-Yang QW, et al. An elevated peripheral blood lymphocyte-to-monocyte ratio predicts favorable response and prognosis in locally advanced breast cancer following neoadjuvant chemotherapy. PLoS One 2014;9(11):e111886

9 Asano Y, Kashiwagi S, Onoda N, et al. Predictive value of neutrophil/lymphocyte ratio for efficacy of preoperative chemotherapy in triple-negative breast cancer. Ann Surg Oncol 2016;23(04): 1104–1110

10 Cuello-López J, Fidalgo-Zapata A, López-Agudelo L, Vásquez-Trespalacios E. Platelet-to-lymphocyte ratio as a predictive factor of complete pathologic response to neoadjuvant chemotherapy in breast cancer. PLoS One 2018;13(11):e0207224

11 Fucà G, Guarini V, Antoniotti C, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer 2020;123(03): 403–409

12 Residual Cancer Burden Calculator [Internet]. MD Anderson Cancer Center. Accessed February 27, 2023 at: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

13 Şahin AB, Cubukcu E, Ocak B, et al. Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. Sci Rep 2021;11(01):14662

14 Lin F, Zhang LP, Xie SY, et al. Pan-immune-inflammation value: a new prognostic index in operative breast cancer. Front Oncol 2022;12:830138

15 Demir H, Demirci A, Eren SK, Beypinar I, Davarcı SE, Baykara M. A new prognostic index in young breast cancer patients. J Coll Physicians Surg Pak 2022;32(01):86–91

16 Li K, Zeng X, Zhang Z, et al. Pan–immune–inflammatory values predict survival in patients after radical surgery for non–metastatic colorectal cancer: a retrospective study. Oncol Lett 2025;29 (04):197

