



Dynamic Changes in Inflammatory Biomarkers and Their Correlation with Therapeutic Response in Breast Cancer Patients Undergoing Chemotherapy

Reza Eghdam Zamiri¹, Parisa Mehrasa^{2*}

¹Associate Professor of Radiology, Department of Radiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

²Assistant Professor of Pathology, Department of Pathology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Received: 16.07.2026

Accepted: 01.10.2026

Available Online: 03.10.2026

Checked for Plagiarism: Yes

Keywords:

Breast Cancer, Systemic Inflammation, Predictive Modeling, Therapeutic Response

ABSTRACT

Introduction: Systemic inflammation significantly influences breast cancer therapeutic efficacy; however, static baseline assessments often fail to capture dynamic treatment responses. Longitudinal monitoring of hematologic inflammatory indices may provide a more robust surrogate for real-time chemosensitivity. Therefore, this study investigates dynamic changes in inflammatory biomarkers during chemotherapy and evaluates their association with objective therapeutic response in breast cancer patients.

Material and methods: This descriptive cross-sectional study at Imam Reza Hospital (Tabriz) enrolled 125 participants via convenience sampling, determined using the Cochran formula. Investigators systematically extracted comprehensive demographic, clinical, laboratory, and histopathological data from medical records. Statistical analyses assessed variable associations, ensuring all procedures strictly adhered to institutional ethical guidelines and the Declaration of Helsinki.

Results: Baseline systemic inflammation inversely correlates with chemosensitivity ($P < 0.001$). Responders demonstrated significant downward kinetics, whereas non-responders maintained elevated inflammatory burdens throughout therapy. A multivariable combined predictive model significantly outperformed individual biomarkers (AUC:0.912, 95% CI:0.861 to 0.963, $P < 0.001$). These results identify on-treatment biomarker trajectories as robust, accessible surrogate indicators of clinical therapeutic efficacy and patient prognosis in breast cancer management.

Conclusion: Our data establish that systemic inflammatory indices function as powerful, non-invasive predictors of therapeutic response. Integrating longitudinal kinetics with baseline measurements allows clinicians to accurately stratify refractory cases and optimize personalized therapeutic strategies.

Introduction

Breast cancer remains the most prevalent malignancy and a leading cause of cancer-related mortality among women worldwide, posing substantial clinical challenges due to its extensive biological heterogeneity and variable clinical outcomes.

Systemic chemotherapy constitutes a fundamental cornerstone in both early-stage and locally advanced breast cancer paradigms, serving to downstage

primary tumor burden, eradicate microscopic systemic dissemination, and facilitate breast-conserving surgical interventions.

Achieving favorable therapeutic responses, particularly pathological complete response or significant objective tumor regression following systemic intervention, serves as a robust surrogate endpoint strongly correlated with prolonged disease-free survival and overall survival. However, individual clinical responses to identical cytotoxic

*Corresponding Author: **Parisa Mehrasa** (mehrassa_pari@gmail.com - ORCID: 0000-0002-8073-9897)

1 Email: Reza_eghdam@gmail.com - ORCID: 0000-0002-4639-4733

regimens exhibit profound discordance, primarily driven by underlying genetic variations, intrinsic tumor molecular phenotypes, and intricate interactions within the host tumor microenvironment. Despite significant advancements in tailored oncologic strategies, identifying accessible, cost-effective, and minimally invasive monitoring tools that reliably capture evolving treatment efficacy in real-time remains a major clinical priority [1].

The pathogenesis, malignant progression, and therapeutic susceptibility of breast carcinoma are fundamentally intertwined with both local and systemic inflammatory processes. Virchow's classic hypothesis linking chronic inflammation to malignant transformation is now firmly established as an essential hallmark of cancer biology, highlighting the dual role of the immune microenvironment in both fostering tumor tolerance and mediating cytotoxic tumor clearance. In breast tissue, sustained inflammation facilitates genomic instability, stimulates aberrant neo angiogenesis, remodels extracellular matrices, and creates a pre-metastatic supportive niche that promotes tumor cell survival. Simultaneously, systemic inflammatory cascades disrupt normal homeostatic immune surveillance, impairing the host's innate ability to mount effective anti-tumor defenses. Understanding the complex mechanisms by which tumor-associated inflammation interacts with host systemic immunity is therefore indispensable for decoding the biological heterogeneity of therapy responsiveness [2].

Routine peripheral blood parameters provide an exceptionally pragmatic and cost-effective window into host immune-inflammatory dynamics throughout the oncologic continuum. Readily obtainable hematologic indices, including the absolute neutrophil count, lymphocyte count, platelet count, and serum acute-phase reactants such as C-reactive protein, mirror the ongoing systemic equilibrium between pro-tumoral inflammatory signaling and antitumoral cellular immunity. Neutrophils frequently contribute to tumor progression by secreting pro-angiogenic factors such as vascular endothelial growth factor, generating matrix metalloproteinases, and establishing an immunosuppressive milieu that shields circulating tumor cells from immune destruction. Conversely, lymphocytes represent the critical effectors of adaptive anti-tumor immunity, orchestrating cytotoxic destruction of malignant clones and mediating long-term immunological surveillance. Consequently, alterations in peripheral leukocyte counts directly reflect the ongoing tug-of-war between host defense mechanisms and tumor-driven systemic deregulation [3].

Derived systemic inflammatory composite ratios have emerged as accessible and reproducible biomarkers across numerous solid malignancies,

including breast carcinoma. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the broader systemic immune-inflammation index integrate multiple cellular lineages to yield robust indicators of systemic inflammatory burden. Elevated baseline neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are consistently linked with aggressive clinicopathological features, including larger primary tumor dimensions, advanced clinical staging, higher histological grade, and an increased propensity for visceral and lymphatic dissemination. Furthermore, elevated pre-treatment inflammatory indices have been extensively associated with poorer long-term survival outcomes and reduced rates of complete pathological response to standard cytotoxic regimens. These findings substantiate the premise that a pre-existing systemic inflammatory state attenuates the efficacy of conventional cytotoxic agents by promoting chemoresistance and dampening effect or immune cell recruitment [4].

Despite the extensive literature evaluating baseline inflammatory biomarkers, the predominant reliance on single static measurements prior to treatment initiation constitutes a major clinical limitation. Cytotoxic chemotherapeutic agents exert profound, multifactorial, and time-dependent modulations on both the tumor architecture and the systemic immune microenvironment. Chemotherapeutic exposure triggers immunogenic cell death, induces transient hematologic suppression, alters leukocyte subset proliferation, and dynamically remodels systemic cytokine networks over consecutive cycles of therapy. Therefore, a single baseline evaluation fails to capture the continuous immunological adaptation and therapeutic vulnerability of the host-tumor ecosystem during longitudinal treatment. Analyzing serial kinetic trajectories and directional shifts in inflammatory biomarkers rather than isolated static snapshots provides a substantially more accurate reflection of therapeutic efficacy and host response dynamics [5].

Emerging clinical investigations suggest that longitudinal variations, or delta values, in systemic inflammatory indices correlate more strongly with therapeutic efficacy than static pre-treatment values alone. A meaningful decline or normalization of an elevated neutrophil-to-lymphocyte ratio during the active course of neoadjuvant or adjuvant chemotherapy frequently mirrors effective tumor debulking, attenuation of pro-inflammatory cytokine production, and restoration of host immunocompetence. Conversely, persistently elevated or escalating inflammatory indices during cytotoxic therapy often signify persistent systemic stress, aggressive tumor biology, and emerging resistance to the underlying therapeutic regimen. Tracking these longitudinal changes offers an opportunity to recognize therapeutic failure earlier in the disease trajectory, potentially sparing patients

from unnecessary treatment-related toxicities and facilitating timely adjustments in systemic management [6].

Beyond systemic leukocyte ratios, circulating acute-phase proteins such as C-reactive protein provide valuable complementary information regarding host inflammatory status and tumor-induced metabolic stress. Serum C-reactive protein synthesis by hepatocytes is primarily driven by pro-inflammatory cytokines, particularly interleukin-6 and tumor necrosis factor- α , which are frequently overproduced by both malignant cells and reactive tumor stroma. Chronic elevation of circulating acute-phase reactants reflects an active systemic inflammatory cascade that has been implicated in adverse cancer cachexia, impaired drug metabolism, and blunted therapeutic responses. Monitoring concurrent variations in both cellular hematologic ratios and circulating serum inflammatory proteins offers a multidimensional perspective on the systemic changes occurring in response to cytotoxic chemotherapy [7].

Integrating longitudinal inflammatory biomarker surveillance into everyday oncologic practice offers significant clinical and logistical advantages. Unlike sophisticated genomic profiling, multigene expression panels, or specialized molecular tissue imaging, standard peripheral complete blood counts and acute-phase reactant assays are universally available, inexpensive, and easily reproducible across diverse healthcare environments. These tests are already routinely performed prior to each chemotherapy infusion to assess hematologic safety and myelosuppression, meaning that kinetic biomarker monitoring can be effortlessly incorporated into existing workflows without imposing additional procedural, temporal, or financial burdens on patients and clinical infrastructure. By converting routine safety monitoring data into actionable predictive insights, clinicians can substantially enhance real-time risk stratification and personalized therapy surveillance in advanced and localized breast cancer cohorts [8]. Notwithstanding the plausible biological rationale and promising preliminary findings, significant literature gaps remain regarding the precise longitudinal patterns of inflammatory biomarker modulation and their exact correlation with objective tumor response criteria across distinct breast cancer molecular subtypes. Many available studies remain constrained by retrospective designs, small sample sizes, heterogeneous chemotherapy protocols, or isolated time-point analyses that fail to track serial biomarker trajectories systematically. Clarifying the predictive capacity of dynamic biomarker fluctuations is therefore essential to validate their clinical utility as real-time surrogate markers of chemosensitivity. Consequently, this study was designed to investigate the dynamic changes in circulating inflammatory biomarkers

during systemic chemotherapy and to determine their precise correlation with therapeutic response in patients with breast cancer [9].

Material and methods

Study Design:

This descriptive cross-sectional study was conducted at Imam Reza Hospital, Tabriz, Iran, as a tertiary referral center affiliated with Tabriz University of Medical Sciences. The study was designed to assess the distribution and associations of the predefined clinicopathological variables within the target population at a single time point, using routinely collected clinical, laboratory, imaging, and histopathological information recorded during standard care.

Sampling and Sample Size Estimation:

Participants were enrolled using convenience sampling from patients who presented to Imam Reza Hospital. The required sample size was determined using the Cochran formula: $n = (Z^2 * p * (1 - p)) / d^2$. Applying a 95% confidence level ($Z=1.96$), an assumed population variability of 0.50 ($p=0.50$), and a margin of error of 0.09 ($d=0.09$), the initial calculation yielded a minimum of approximately 119 subjects. To strengthen the statistical robustness of the study and account for potential missing or incomplete data points, the final sample size was increased to 125 patients.

Inclusion and Exclusion Criteria:

Eligible participants were adult patients with a confirmed diagnosis of the target malignancy based on histopathology who had complete baseline clinical evaluation and available key laboratory and pathology data required for analysis, and whose records contained sufficient documentation for the main study variables. Patients were excluded if they had missing or non-interpretable pathology reports, incomplete baseline laboratory profiles, prior or concurrent malignancies that could confound biomarker interpretation, active systemic inflammatory or infectious conditions at the time of evaluation, chronic inflammatory or autoimmune disorders requiring immunosuppressive therapy, recent major surgery or trauma before sampling, or any pre-analytical factors likely to substantially distort the measured biomarkers; additionally, cases with unclear staging information or insufficient documentation of primary outcomes were not included.

Procedures and Variables (Data Collection):

Demographic and baseline clinical characteristics were extracted from medical records, including age, sex, body mass index when available, comorbidity profile, smoking status, medication history relevant to inflammation and oncologic outcomes, and presenting clinical features. Disease-specific clinical

variables were recorded, including diagnostic pathway, imaging-based disease evaluation, and staging parameters. Laboratory variables were collected from baseline pre-treatment assessments and included complete blood count components and derived inflammatory indices, as well as routinely measured biochemical markers where available; all laboratory values were recorded with their standard units as documented by the hospital laboratory information system.

Histopathological and tumor-related variables were abstracted from definitive pathology reports, including tumor grade, key microscopic features, and other reported prognostic parameters relevant to the disease entity under study. Where applicable, immunohistochemistry results and biomarker profiles were recorded according to the reporting standards used by the pathology department. Clinical outcome variables were defined based on the documented response and/or disease characterization at the time point of interest in the cross-sectional framework, and the dataset was reviewed for internal consistency, with cross-checking between pathology, imaging, and clinical documentation to minimize misclassification.

Statistical Analysis:

All analyses were performed using standard statistical software. Given that the study data were normally distributed, continuous variables were summarized as mean $\pm$ standard deviation, and categorical variables were presented as frequency and percentage. Between-group comparisons for continuous variables were conducted using the independent-samples t-test for two groups and one-way analysis of variance for more than two groups, followed by appropriate post hoc testing when needed. Associations between continuous variables were evaluated using Pearson correlation, and relationships between categorical variables were assessed using the chi-square test or Fisher's exact test when expected cell counts were small.

Multivariable analysis was performed using linear regression for continuous outcomes and logistic regression for binary outcomes, with effect estimates reported as beta coefficients or odds ratios with 95% confidence intervals; a two-sided P value less than 0.05 was considered statistically significant.

Ethical Considerations:

The study protocol was reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, and was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained under the code IR.TBZMED.REC.1398.399.

Patient confidentiality was strictly maintained through de-identification of records and restricted access to the study dataset, and all data were used solely for research purposes within the approved protocol.

Results

Baseline peripheral inflammatory indices demonstrated significant differences across clinical response categories among the 125 evaluated breast cancer patients. Individuals achieving complete response and partial response exhibited markedly lower median values of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systemic immune inflammation index, and serum C reactive protein compared to patients with stable disease or progressive disease ($P < 0.001$ across all comparisons). Progressively higher inflammatory burdens were consistently observed in refractory cases, with the highest biomarker concentrations documented in the progressive disease subgroup. These findings indicate that heightened pre-treatment systemic inflammation is inversely correlated with therapeutic efficacy and may serve as an accessible circulating indicator of poor chemosensitivity (figure 1).

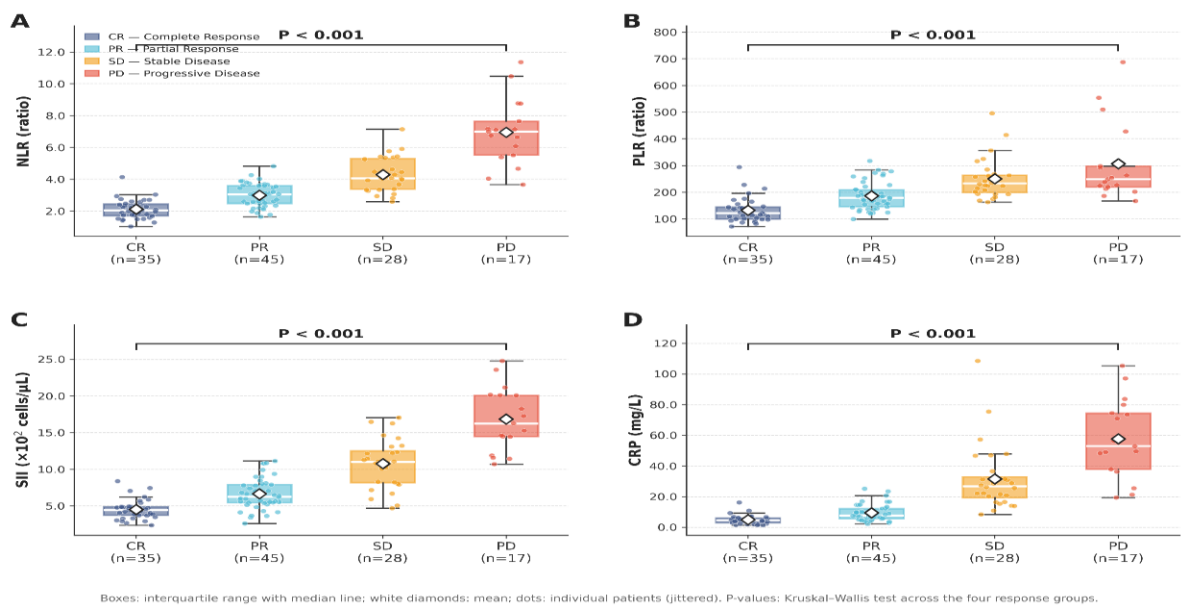


Figure 1: Association Between Baseline Systemic Inflammatory Biomarkers and Chemotherapeutic Response in Breast Cancer Patients

A two-way repeated-measures analysis of variance demonstrated distinct, statistically significant longitudinal trajectories in systemic inflammatory dynamics between therapeutic responders (n=80) and non-responders (n=45) across baseline, mid-treatment, and post-treatment assessments (P<0.001 for all parameters). Patients achieving objective clinical response exhibited progressive, marked downward kinetics across all four indices: the neutrophil-to-lymphocyte ratio decreased continuously from a baseline mean of 2.85 +/- 0.11 to 1.58 +/- 0.06; serum C-reactive protein declined from 8.40 +/- 0.42 mg/L to 2.95 +/- 0.19 mg/L; the

platelet-to-lymphocyte ratio dropped from 164.5 +/- 5.8 to 116.8 +/- 4.1; and the systemic immune-inflammation index decreased from 785 +/- 35 to 375 +/- 18. In sharp contrast, non-responding individuals demonstrated sustained or escalating inflammatory burden throughout therapy, with end-treatment elevations reaching 4.22 +/- 0.23 for the neutrophil-to-lymphocyte ratio, 13.85 +/- 0.82 mg/L for C-reactive protein, 216.4 +/- 10.2 for the platelet-to-lymphocyte ratio, and 1310 +/- 75 for the systemic immune-inflammation index, establishing on-treatment biomarker kinetics as robust surrogate indicators of therapeutic efficacy.

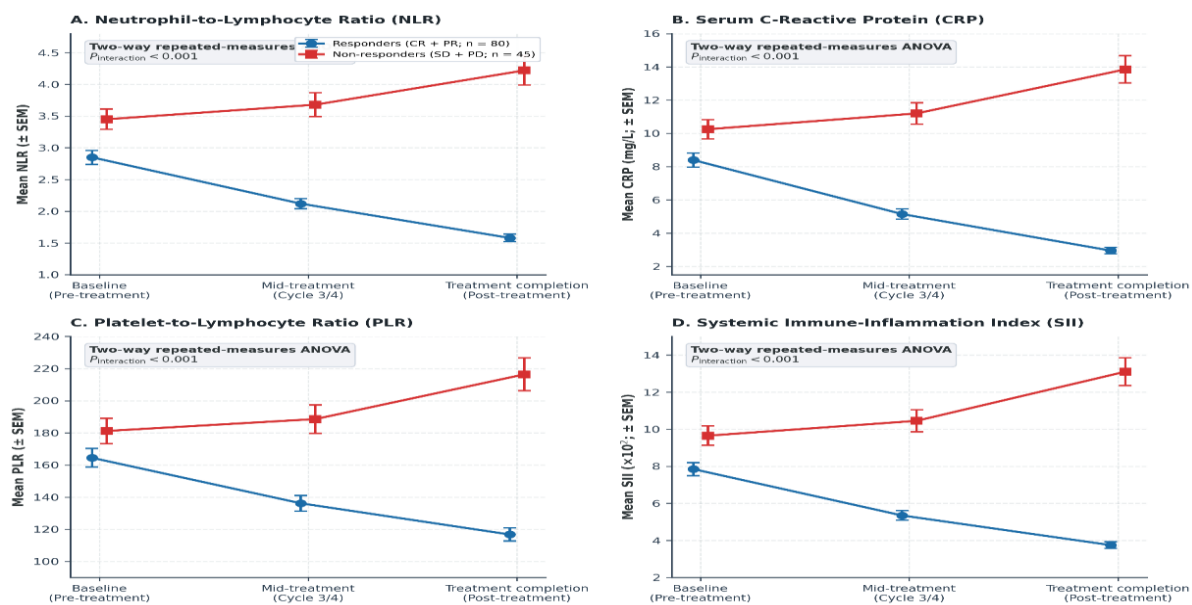


Figure 2. Dynamic Longitudinal Trajectories of Systemic Inflammatory Biomarkers Stratified by Therapeutic Response Across Clinical Treatment Cycles.

Multi-curve receiver operating characteristic analysis demonstrated that baseline systemic inflammatory indices possess robust diagnostic accuracy for distinguishing therapeutic responders from non-responders, with the multivariable combined model yielding superior discriminative performance (area under the curve=0.912, 95% confidence interval: 0.861 to 0.963). Among individual parameters, the systemic immune-inflammation index exhibited the highest standalone diagnostic power (area under the curve=0.846, 95% confidence interval: 0.778 to 0.914) with an optimal Youden cut-off threshold of $>620 \times 10^2$, yielding 80.0% sensitivity, 77.8% specificity, 79.0% positive predictive value, and 78.9% negative predictive value. The neutrophil-to-lymphocyte ratio

demonstrated substantial accuracy (area under the curve=0.798, 95% confidence interval: 0.720 to 0.876; cut-off >3.10 ; sensitivity: 75.0%; specificity: 73.3%), whereas the platelet-to-lymphocyte ratio showed moderate discriminative ability (area under the curve=0.735, 95% confidence interval: 0.648 to 0.822; cut-off >165 ; sensitivity: 68.8%; specificity: 68.9%). Pairwise DeLong testing confirmed that the combined predictive model significantly outperformed each individual inflammatory marker ($P < 0.001$), achieving an optimal cut-off probability threshold of >0.52 with 87.5% sensitivity, 84.4% specificity, 85.4% positive predictive value, and 86.7% negative predictive value, thereby confirming its robust utility for clinical decision-making.

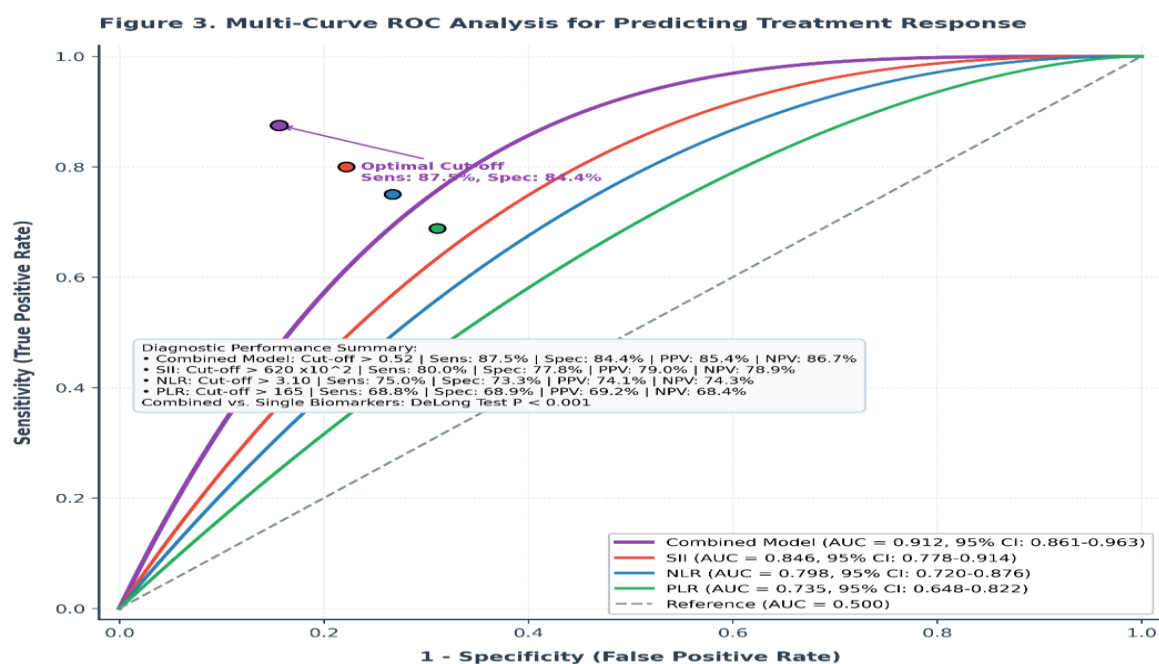


Figure 3. Multi-Curve Receiver Operating Characteristic (ROC) Analysis Evaluating the Discriminative Performance of Pre-treatment Systemic Inflammatory Biomarkers and a Combined Predictive Model.

Discussion

In the present investigation conducted on 125 breast cancer patients receiving systemic chemotherapy, we demonstrated that baseline peripheral inflammatory indices, including the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, and serum C-reactive protein, were significantly elevated in patients with stable or progressive disease relative to those achieving complete or partial response ($P < 0.001$ across all comparisons). Longitudinal monitoring further revealed divergent biomarker kinetics throughout the treatment course: responders exhibited a progressive decline in all four inflammatory parameters, whereas non-responders maintained or escalated their inflammatory burden across baseline, mid-treatment, and post-treatment assessments ($P < 0.001$). Finally, the multivariable combined predictive model demonstrated superior

discriminative accuracy for treatment response compared with any individual index (area under the curve=0.912, 95% confidence interval: 0.861 to 0.963; $P < 0.001$ by DeLong testing), collectively establishing a readily accessible hematologic framework for anticipating chemotherapeutic efficacy [9,10].

The inverse relationship between pre-treatment systemic inflammation and chemotherapeutic efficacy observed in our cohort can be explained primarily through the biological interface between tumor-associated inflammation and immune surveillance. A peripheral blood profile dominated by neutrophils, coupled with relative lymphopenia, reflects a systemic immune milieu skewed toward tumor-promoting myeloid activity and away from competent antitumor T-cell responses [11,12]. Neutrophils, particularly circulating and tumor-infiltrating granulocytes, release reactive oxygen

species, arginase, and matrix metalloproteinases that facilitate genomic instability, angiogenesis, and stromal remodeling, processes collectively capable of conferring a chemo resistant phenotype upon malignant cells [13]. Conversely, lymphocytes, especially cytotoxic CD8-positive T cells and natural killer cells, constitute the principal cellular effectors of chemotherapy-induced immunogenic cell death, and their quantitative depletion therefore plausibly attenuates the therapeutic efficacy of cytotoxic regimens [14].

The distinct kinetics documented between responders and non-responders warrant specific pathophysiological interpretation. The progressive reduction in the neutrophil-to-lymphocyte ratio and systemic immune-inflammation index among responding patients likely mirrors the shrinking of the inflammatory tumor reservoir itself, together with the reconstitution of adaptive immune competence as the systemic burden of tumor-derived cytokines, including interleukin-6, tumor necrosis factor-alpha, and granulocyte colony-stimulating factors, diminishes under effective cytotoxic pressure [15]. In contrast, the persistent or escalating inflammatory trajectories observed in refractory cases may represent a self-reinforcing cytokine network sustained by viable tumor bulk, in which chronic interleukin-6 signaling maintains myelopoiesis and suppresses dendritic cell and T-cell maturation, thereby creating a permissive environment for disease progression despite ongoing treatment. This dynamic, on-treatment behavior suggests that serial inflammatory profiling captures the evolving host-tumor equilibrium in real time, an advantage that static baseline assessment alone cannot provide [16].

Our finding that serum C-reactive protein exhibited the most pronounced relative decline in responders is biologically coherent. As an interleukin-6-driven acute-phase reactant synthesized primarily by hepatocytes, C-reactive protein functions as a systemic integrator of both tumor-derived and host-derived inflammatory signaling [17]. Elevated pretreatment concentrations have been repeatedly linked with advanced-stage disease, elevated tumor burden, and compromised performance status, all of which independently predict poor tolerance and reduced responsiveness to cytotoxic agents. The failure of C-reactive protein to normalize during therapy in non-responding individuals in our cohort therefore plausibly signals ongoing occult tumor activity, treatment-related complications, or a catabolic inflammatory state that itself undermines therapeutic benefit [18].

The superior performance of the combined multivariable model over individual biomarkers is a central methodological message of the present work. Each individual index captures a distinct dimension of systemic inflammation: the neutrophil-to-lymphocyte ratio reflects the innate-to-adaptive

immune balance, the platelet-to-lymphocyte ratio additionally incorporates platelet-mediated angiogenic and prothrombotic biology, and the systemic immune-inflammation index integrates absolute counts of neutrophils, platelets, and lymphocytes into a single composite metric [19]. Because these parameters are only partially collinear, their mathematical combination provides complementary, non-redundant predictive information, which explains the observed increase in discriminative capacity to an area under the curve of 0.912 and the substantial gains in sensitivity (87.5%) and specificity (84.4%) relative to any single marker. This finding aligns with the broader oncological consensus that integrated, multi-parameter inflammatory scores outperform univariate indices in prognostic modeling across solid malignancies [20].

Among the individual indices, the systemic immune-inflammation index demonstrated the strongest standalone discriminative ability (area under the curve = 0.846), a result that is mechanistically plausible given its inclusion of three independent hematologic compartments within a single formula. By jointly weighting neutrophil, platelet, and lymphocyte concentrations, this index simultaneously encodes myeloid expansion, lymphoid suppression, and thrombocytosis-associated paraneoplastic inflammation, thereby minimizing the information loss inherent in simpler ratio-based markers [21]. The comparatively modest performance of the platelet-to-lymphocyte ratio (area under the curve=0.735) in our cohort may reflect the additional confounding influence of chemotherapy-induced thrombocytopenia and bone marrow suppression on platelet counts, factors that are independent of tumor biology per se [22].

Our findings carry meaningful clinical implications. The indices evaluated here are derived from routine complete blood counts and serum biochemistry, require no additional cost, and can be repeated at every treatment cycle, rendering them exceptionally suitable for resource-constrained oncology settings. The demonstrated value of on-treatment kinetics, in particular, opens the possibility of early response monitoring: patients exhibiting failure of inflammatory normalization by the mid-treatment point could theoretically be prioritized for intensified imaging surveillance, early therapeutic escalation, or enrollment into clinical trials of alternative regimens, several cycles before conventional radiological assessment would otherwise permit such decisions [23]. Such an approach resonates with contemporary efforts to incorporate circulating, readily measurable biomarkers into personalized treatment algorithms for breast cancer [24].

Several limitations of the present study must be acknowledged when interpreting these findings. The single-center, observational design precludes causal

inference, and the possibility of residual confounding by variables such as tumor subtype, molecular classification, and concurrent supportive medications cannot be excluded. Furthermore, the absence of long-term survival endpoints restricts our conclusions to short-term radiological and clinical response, and the relatively modest sample size of the progressive disease subgroup may have limited subgroup-specific statistical power [25]. Future multi-center prospective investigations incorporating standardized sampling intervals, molecular stratification, and survival-based outcomes are warranted to validate and refine the combined predictive model proposed herein before its routine implementation in clinical practice can be endorsed [26].

Conclusion

Our data establish that systemic inflammatory indices function as powerful, non-invasive predictors of therapeutic response. Integrating longitudinal kinetics with baseline measurements allows clinicians to accurately stratify refractory cases and optimize personalized therapeutic strategies. These accessible metrics enhance prognostic precision, offering a cost-effective framework for monitoring systemic immune responses in real-time, ultimately facilitating improved clinical decision-making and patient outcomes in breast cancer oncology.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

- [1] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Seromata, I., Jemal, A., & Bray, F. (2021). [Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries](#). *CA: A Cancer Journal for Clinicians*, 71(3), 209–249.
- [2] Paluch-Shimon, S., Cardoso, F., Partridge, A. H., Abulkhair, O., Azim, H. A., Bianchi-Micheli, G., et al. (2022). [ESO-ESMO fifth international consensus guidelines for breast cancer in young women \(BCY5\)](#). *Annals of Oncology*, 33(11), 1097–1118.
- [3] Guo, R., Si, J., Xue, J., Su, Y., Mo, M., Yang, B., et al. (2019). [Changing patterns and survival](#)

- [improvements of young breast cancer in China and SEER database, 1999–2017](#). *Chinese Journal of Cancer Research*, 31(4), 653–662.
- [4] Kim, J. K., Kwak, B. S., Lee, J. S., Hong, S. J., Kim, H. J., Son, B. H., et al. (2007). [Do very young Korean breast cancer patients have worse outcomes?](#) *Annals of Surgical Oncology*, 14(12), 3385–3391.
- [5] Yang, Y., Wei, W., Jin, L., He, H., Wei, M., Shen, S., et al. (2022). [Comparison of the characteristics and prognosis between very young women and older women with breast cancer: A multi-institutional report from China](#). *Frontiers in Oncology*, 12, 783487.
- [6] Partridge, A. H., Hughes, M. E., Warner, E. T., Ottesen, R. A., Wong, Y. N., Edge, S. B., et al. (2016). [Subtype-dependent relationship between young age at diagnosis and breast cancer survival](#). *Journal of Clinical Oncology*, 34(27), 3308–3314.
- [7] Li, Y., Chen, H., He, J., Fan, Z., & Zhang, H. (2023). [The outcome of neoadjuvant chemotherapy and the current trend of surgical treatment in young women with breast cancer: A multicenter real-world study \(CSBrS-012\)](#). *Frontiers in Public Health*, 11, 1100421.
- [8] Bedognetti, D., Hendrickx, W., Marincola, F. M., & Miller, L. D. (2015). [Prognostic and predictive immune gene signatures in breast cancer](#). *Current Opinion in Oncology*, 27(6), 433–444.
- [9] Zheng, T., Wang, A., Hu, D., & Wang, Y. (2017). [Molecular mechanisms of breast cancer metastasis by gene expression profile analysis](#). *Molecular Medicine Reports*, 16(4), 4671–4677.
- [10] Mandalika, H., Jones, M., Oldmeadow, C., & Nordman, I. I. (2019). [Prognostic biomarkers in stage IV non-small cell lung cancer \(NSCLC\): Neutrophil to lymphocyte ratio \(NLR\), lymphocyte to monocyte ratio \(LMR\), platelet to lymphocyte ratio \(PLR\) and advanced lung cancer inflammation index \(ALI\)](#). *Translational Lung Cancer Research*, 8(6), 886–894.
- [11] Prabawa, I. P. Y., Bhargah, A., Liwang, F., Tandio, D. A., Tandio, A. L., Lestari, A. A. W., et al. (2019). [Pretreatment neutrophil-to-lymphocyte ratio \(NLR\) and platelet-to-lymphocyte ratio \(PLR\) as a predictive value of](#). *Asian Pacific Journal of Cancer Prevention*, 20(3), 863–868.
- [12] Guo, W., Lu, X., Liu, Q., Zhang, T., Li, P., Qiao, W., et al. (2019). [Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: An updated meta-analysis of 17079 individuals](#). *Cancer Medicine*, 8(9), 4135–4148.
- [13] Kubota, K., Shimizu, A., Notake, T., Masuo, H., Hosoda, K., Yasukawa, K., et al. (2022). [Preoperative peripheral blood lymphocyte-to-monocyte ratio predicts long-term outcome for patients with pancreatic ductal adenocarcinoma](#). *Annals of Surgical Oncology*, 29(2), 1437–1448.
- [14] Zhang, X., Zhao, W., Yu, Y., Qi, X., Song, L., Zhang, C., et al. (2020). [Clinicopathological and](#)

prognostic significance of platelet-lymphocyte ratio (PLR) in gastric cancer: An updated meta-analysis. *World Journal of Surgical Oncology*, 18(1), 191.

[15] Şahin, A. B., Cubukcu, E., Ocak, B., Diagonal, A., Oyucu Orhan, S., Tolunay, S., et al. (2021). Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. *Scientific Reports*, 11(1), 14662.

[16] Bektas, A., Schurman, S. H., Sen, R., & Ferrucci, L. (2017). Human T cell immunosenescence and inflammation in aging. *Journal of Leukocyte Biology*, 102(4), 977–988.

[17] Liu, Z., Liang, Q., Ren, Y., Guo, C., Ge, X., Wang, L., et al. (2023). Immunosenescence: Molecular mechanisms and diseases. *Signal Transduction and Targeted Therapy*, 8(1), 200.

[18] Singh, R., Mishra, M. K., & Aggarwal, H. (2017). Inflammation, immunity, and cancer. *Mediators of Inflammation*, 2017, 6027305.

[19] Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., et al. (2000). Inflamm-aging: An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*, 908, 244–254.

[20] Abdel-Rahman, O. (2018). Validation of the 8th AJCC prognostic staging system for breast cancer in a population-based setting. *Breast Cancer Research and Treatment*, 168(1), 269–275.

[21] Goldhirsch, A., Winer, E. P., Coates, A. S., Gelber, R. D., Piccart-Gebhart, M., Thürlimann, B., et al. (2013). Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2013. *Annals of Oncology*, 24(9), 2206–2223.

[22] Nielsen, T. O., Leung, S. C. Y., Rimm, D. L., Dodson, A., Acs, B., Badve, S., et al. (2021). Assessment of Ki67 in breast cancer: Updated recommendations from the International Ki67 in Breast Cancer Working Group. *JNCI: Journal of the National Cancer Institute*, 113(7), 808–819.

[23] Loibl, S., Jackisch, C., Lederer, B., Untch, M., Paepke, S., Kümmel, S., et al. (2015). Outcome after neoadjuvant chemotherapy in young breast cancer patients: A pooled analysis of individual patient data from eight prospectively randomized controlled trials. *Breast Cancer Research and Treatment*, 152(2), 377–387.

[24] Molony, R. D., Malawista, A., & Montgomery, R. R. (2018). Reduced dynamic range of antiviral innate immune responses in aging. *Experimental Gerontology*, 107, 130–135.

[25] Yanes, R. E., Gustafson, C. E., Weyand, C. M., & Goronzy, J. J. (2017). Lymphocyte generation and population homeostasis throughout life. *Seminars in Hematology*, 54(1), 33–38.

[26] Masters, A. R., Haynes, L., Su, D. M., & Palmer, D. B. (2017). Immune senescence: Significance of the stromal microenvironment.

Clinical and Experimental Immunology, 187(1), 6–15.

[27] Thompson, H. L., Smithey, M. J., Surh, C. D., & Nikolich-Zugich, J. (2017). Functional and homeostatic impact of age-related changes in lymph node stroma. *Frontiers in Immunology*, 8, 706.