Med. Psychol. Health Res. J. **(2026),** Volume 2, Issue 5, 329-338

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2026.586290.1100

Prognostic Value and Predictive Utility of CA15-3 and CRP as Pathophysiological Biomarkers in Patients with Breast Cancer Undergoing Chemotherapy

Parisa Mehrasa [1], Reza Eghdam Zamiri[2*]

[1]Assistant Professor of Pathology, Department of Pathology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Associate Professor of Radiology, Department of Radiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Received: 28.03.2026
Accepted: 13.06.2026
Available Online: 18.06.2026
Checked for Plagiarism: Yes

Keywords:
Breast cancer, CA15-3, C-reactive protein, Chemotherapy, Biomarkers.

ABSTRACT

Introduction: Breast cancer outcomes vary widely, creating a need for accessible biomarkers that reflect tumor burden and systemic inflammation during chemotherapy. CA15-3 and CRP may provide complementary prognostic and predictive information. This study aims to evaluate the prognostic value and predictive utility of CA15-3 and CRP in patients with breast cancer undergoing chemotherapy.

Material and methods: This descriptive cross-sectional study will be conducted at Shahid Madani Hospital, Tabriz University of Medical Sciences, using convenience sampling to enroll 70 breast cancer patients undergoing chemotherapy. Demographic, clinicopathological, and treatment data, along with serum CA15-3 and CRP levels, will be collected and analyzed using appropriate descriptive and inferential statistics.

Results: In 70 patients with breast cancer undergoing chemotherapy, the mean age was 49.8 ± 10.7 years; 80.0% had invasive ductal carcinoma, 70.0% had lymph node involvement, and 18.6% had metastasis. Median CA15-3 and CRP levels were 31.5 U/mL and 8.9 mg/L, respectively.

Conclusion: These findings indicate that CA15-3 and CRP reflect related but non-identical biological dimensions in patients with breast cancer undergoing chemotherapy. While CA15-3 appears to represent tumor-associated activity, CRP likely captures the accompanying systemic inflammatory response.

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality despite substantial progress in screening, molecular classification, systemic therapy, and supportive care. Its clinical course is remarkably heterogeneous, ranging from indolent localized disease to rapidly progressive metastatic cancer, and this diversity has made risk stratification central to modern management. In routine practice, prognostic assessment relies on a combination of tumor stage, histologic grade, lymph node involvement, hormone receptor status, HER2 expression, proliferation indices, and increasingly, multigene signatures.

Yet these tools do not fully capture the dynamic biological changes that occur during treatment, especially in patients receiving chemotherapy. There is therefore growing interest in readily accessible circulating biomarkers that can complement established clinic pathologic factors, reflect ongoing tumor behavior, and provide early signals of treatment response or resistance. Among the candidate laboratory markers, cancer antigen 15-3 (CA15-3) and C-reactive protein (CRP) have attracted particular attention because they are inexpensive, widely available, and biologically linked to tumor burden and host inflammatory responses, respectively.

Corresponding Author:* ***Reza Eghdam Zamiri* *(reza_zamiri@gmail.com - ORCID: 0000-0002-4639-4733)*
1 Email: mehrasa_pari@gmail.com ORCID: 0000-0002-8073-9897)

Their combined evaluation may offer a practical framework for understanding both malignant activity and the systemic pathophysiological environment in which breast cancer progresses and responds to treatment (1).

Chemotherapy continues to occupy a major role in the management of breast cancer across neoadjuvant, adjuvant, and metastatic settings, even in the era of targeted therapy and immunomodulatory approaches. In early-stage disease, chemotherapy is often used to reduce recurrence risk and eradicate micro metastatic disease, whereas in locally advanced and metastatic settings it remains essential for disease control, symptom palliation, and prolongation of survival. However, response to chemotherapy is variable, and treatment is accompanied by substantial physical, psychological, and economic costs. Clinicians therefore face a persistent challenge: identifying patients most likely to benefit from a given regimen while minimizing exposure to ineffective or unnecessarily toxic therapy. Imaging and pathological assessment remain important standards for response evaluation, but they may not always capture subtle biological shifts early enough to guide timely therapeutic decisions. Laboratory biomarkers that can be serially measured during treatment may help bridge this gap by offering a less invasive and potentially more immediate view of disease dynamics. In this context, biomarkers with both prognostic and predictive relevance are especially valuable because they may inform baseline risk while also anticipating therapeutic outcomes under chemotherapy (2).

CA15-3 is one of the most extensively studied serum tumor markers in breast cancer and is derived from circulating epitopes of MUC1, a transmembrane glycoprotein that is overexpressed and aberrantly glycosylated in many epithelial malignancies. In breast cancer, increased shedding of MUC1-related antigens into the circulation is thought to reflect tumor burden, biological aggressiveness, and metastatic activity, particularly in advanced disease. Although CA15-3 is not sufficiently sensitive or specific for population screening or for the diagnosis of early-stage disease, it has been used in selected clinical contexts for disease monitoring and surveillance. Elevated serum CA15-3 levels have been associated with larger primary tumors, nodal involvement, distant metastasis, and unfavorable outcomes in several observational studies. Furthermore, dynamic changes in CA15-3 during treatment may correlate with response trajectories, making this biomarker of particular interest in patients receiving systemic therapy. Nonetheless, the precise role of CA15-3 remains debated, partly because its interpretation can be influenced by tumor subtype, disease extent, assay variability, and timing of measurement. These uncertainties underscore the need for context-specific prospective evaluation, particularly in relation to chemotherapy response and prognosis (3).

Beyond tumor-derived markers, the inflammatory state of the host has emerged as a major determinant of cancer progression and treatment outcomes. CRP, an acute-phase reactant synthesized predominantly by hepatocytes under stimulation from interleukin-6 and other proinflammatory cytokines, represents one of the most widely used clinical indicators of systemic inflammation. In oncology, elevated CRP has been associated with poorer survival across multiple malignancies, supporting the concept that inflammation is not merely a bystander phenomenon but a biologically active contributor to tumor development, angiogenesis, immune evasion, and metastatic spread. In breast cancer, chronic low-grade systemic inflammation may arise from tumor-host interactions, treatment-related tissue injury, comorbid conditions, adiposity, and other factors that shape the disease microenvironment. Because chemotherapy itself can modulate inflammatory pathways, serial CRP assessment may provide insights into both baseline pathophysiological status and treatment-associated biological changes. Importantly, CRP may capture dimensions of disease behavior not reflected by tumor-specific markers alone, particularly the systemic response that influences resilience, toxicity, and progression. This makes CRP a compelling companion biomarker to CA15-3 in studies seeking to integrate tumor burden with host inflammatory biology (4).

The pathophysiological rationale for jointly examining CA15-3 and CRP in breast cancer is strong. CA15-3 principally reflects properties of the tumor, including cellular turnover, mucin expression, and disease dissemination, whereas CRP reflects the host's inflammatory and acute-phase response to malignant and nonmalignant stimuli. Cancer progression is increasingly understood as the product of reciprocal interactions between tumor cells and the surrounding microenvironment, involving cytokine signaling, stromal remodeling, angiogenesis, and immune regulation. These processes contribute not only to clinical progression but also to therapeutic sensitivity or resistance. A patient with elevated CA15-3 may have substantial tumor burden, but if CRP is also high, this may indicate a biologically aggressive context characterized by amplified systemic inflammation and potentially less favorable response to treatment. Conversely, discordance between these biomarkers may reveal distinct disease states with different prognostic implications. Evaluating them together may therefore improve patient stratification beyond what either marker can achieve in isolation and may help identify clinically meaningful phenotypes among individuals undergoing chemotherapy (5).

From a prognostic perspective, biomarkers are valuable when they identify differences in clinical

outcomes independent of treatment, including recurrence, progression, or survival. From a predictive perspective, they are useful when they indicate the likelihood of response or lack of response to a particular therapeutic intervention. Distinguishing between these two functions is critical, yet many biomarker studies in breast cancer conflate them or rely on retrospective analyses that are vulnerable to selection bias, inconsistent sampling intervals, and incomplete adjustment for confounders. A prospective design offers a more rigorous framework by enabling predefined biomarker measurement, standardized follow-up, and temporal alignment between biomarker changes and clinical events. In patients receiving chemotherapy, this approach is particularly important because biomarker fluctuations may precede radiological or pathological evidence of response. The prospective assessment of CA15-3 and CRP could therefore clarify whether baseline values, on-treatment trajectories, or combined biomarker patterns are associated with subsequent outcomes such as objective response, recurrence risk, progression-free survival, or overall survival. Such evidence could strengthen the clinical interpretability of these markers and define their practical utility in treatment monitoring (6).

Existing literature provides encouraging but incomplete evidence regarding the individual roles of CA15-3 and CRP in breast cancer. Studies of CA15-3 have often shown associations with metastatic disease and recurrence, but its performance in early response evaluation remains inconsistent, with some investigations reporting meaningful correlations with treatment efficacy and others demonstrating limited discriminatory value. Similarly, elevated CRP has repeatedly been linked to adverse outcomes, yet its specificity for cancer-related inflammation is inherently limited, and levels may be influenced by infection, metabolic disturbances, autoimmune disorders, or other comorbidities. Moreover, relatively few studies have prospectively assessed these two markers together in a clearly defined chemotherapy-treated breast cancer population. This gap is important because the integration of a tumor-associated marker with an inflammatory marker may be more informative than either alone, especially in a disease as heterogeneous as breast cancer. Clarifying their combined prognostic and predictive value may help address a practical clinical question: can simple serum biomarkers provide incremental information that supports individualized therapeutic decision-making during chemotherapy? (7)

Another important consideration is the increasing emphasis on accessible and scalable biomarkers in routine oncology practice. While genomic assays, circulating tumor DNA, and advanced imaging techniques have transformed cancer research and precision medicine, their availability remains uneven across health systems, and cost can limit widespread implementation. In contrast, CA15-3 and CRP are measurable with standard laboratory infrastructure and can be repeated serially with minimal patient burden. This accessibility is particularly relevant in resource-constrained settings, where clinicians may need affordable tools to support risk assessment and longitudinal monitoring. Even in high-resource environments, simple biomarkers retain value if they can provide rapid, reproducible, and clinically actionable information. A well-designed prospective study evaluating CA15-3 and CRP in patients undergoing chemotherapy may therefore have implications beyond academic interest; it may contribute to a pragmatic model of biomarker-informed care that is more feasible for broad implementation. Such a model would be especially useful if biomarker trends could identify high-risk patients who require closer surveillance or earlier treatment modification (8).

The biological behavior of breast cancer under chemotherapy is influenced by molecular subtype, disease stage, treatment intent, and host factors, all of which may interact with serum biomarker profiles. Hormone receptor-positive disease, HER2-positive tumors, and triple-negative breast cancer differ substantially in proliferation rate, metastatic pattern, immune milieu, and sensitivity to systemic therapy. Likewise, biomarker kinetics may differ between neoadjuvant, adjuvant, and metastatic treatment settings. These complexities highlight the need for careful interpretation of CA15-3 and CRP within a clinically characterized cohort. Prospective investigation can help determine whether these markers retain significance after accounting for standard prognostic variables and whether their association with outcomes is consistent across subgroups or concentrated in specific biological contexts. Such findings would not only improve their clinical relevance but also enhance understanding of how tumor-derived and inflammation-related signals interact during the course of treatment. In this regard, biomarker research can serve both translational and practical aims by linking measurable laboratory parameters to the underlying pathophysiology of disease evolution under chemotherapy (9).

Given these considerations, the evaluation of CA15-3 and CRP as pathophysiological biomarkers in breast cancer patients receiving chemotherapy is timely and clinically meaningful. A prospective study design allows for systematic exploration of whether these markers can capture complementary aspects of disease burden and host response, whether they can stratify prognosis at baseline, and whether their changes over time can predict therapeutic outcomes. If validated, this biomarker combination could support more individualized management by identifying patients with

biologically aggressive disease, facilitating early recognition of inadequate response, and informing follow-up strategies during and after treatment. At the same time, rigorous analysis is necessary to distinguish true clinical utility from statistical association and to determine how these markers should be interpreted alongside established prognostic factors. The ultimate goal is not to replace existing tools, but to refine them through integration with simple, biologically plausible laboratory measures. In this framework, CA15-3 and CRP represent a promising pair of candidate biomarkers whose combined assessment may advance the prognostic and predictive evaluation of breast cancer in the setting of chemotherapy.

Material and methods

Study Design

This descriptive cross-sectional study will be conducted at Shahid Madani Hospital, affiliated with Tabriz University of Medical Sciences, Tabriz, Iran. The study is designed to evaluate the prognostic value and predictive utility of the laboratory biomarkers CA15-3 and C-reactive protein (CRP) in patients with breast cancer undergoing chemotherapy. All eligible patients presenting during the study period and meeting the predefined selection criteria will be assessed in a standardized manner. The cross-sectional framework will allow the simultaneous evaluation of clinic pathological characteristics, treatment-related variables, and serum biomarker levels in the study population at the time of assessment. All study procedures, laboratory measurements, and data collection steps will be performed according to a predefined protocol to ensure consistency and reproducibility.

Inclusion and Exclusion Criteria

The study population will consist of patients with a confirmed diagnosis of breast cancer who are undergoing chemotherapy at Shahid Madani Hospital during the study period. Inclusion criteria will include age 18 years or older, histopathologically confirmed breast cancer, receipt of chemotherapy according to the treating oncologist's plan, availability of essential clinical and pathological data in the medical record, and willingness to participate in the study by providing written informed consent. Patients will be included regardless of molecular subtype, provided that their diagnosis and treatment course are adequately documented. Exclusion criteria will include refusal to participate, incomplete clinical or laboratory records, presence of active acute infection at the time of assessment, documented chronic inflammatory or autoimmune disease that may significantly affect CRP levels, severe hepatic or renal failure, concurrent diagnosis of another active malignancy, and any condition judged by the investigators to interfere with accurate interpretation of biomarker measurements. Patients receiving chemotherapy but lacking valid serum CA15-3 or CRP results within the defined study time window will also be excluded from the final analysis.

Sampling Method and Sample Size

Sampling will be performed using a convenience sampling method. All eligible patients with breast cancer undergoing chemotherapy who attend the study setting during the recruitment period and satisfy the inclusion criteria will be consecutively enrolled until the required sample size is reached. The final sample size will be 70 patients. Sample size estimation will be based on the sample size estimation formula for descriptive cross-sectional studies, using the standard formula based on prevalence estimation. The variables of this formula include the confidence level, the corresponding standard normal deviate, the estimated proportion or prevalence of the primary variable of interest, and the acceptable margin of error or precision. This approach is suitable for determining the minimum number of participants required to obtain statistically acceptable estimates in a cross-sectional design.

Study Procedure

After obtaining ethical approval and administrative permission, patient recruitment will begin in the oncology-related units and outpatient services of Shahid Madani Hospital. Potentially eligible patients will first be screened through review of medical records and consultation with the treating oncology team. For each patient, demographic data will be recorded, including age, sex, marital status if available, and relevant clinical background information. Disease-related variables will then be extracted from the medical file, including date of diagnosis, histopathological type, tumor grade, stage of disease, lymph node status, presence or absence of metastasis, estrogen receptor status, progesterone receptor status, HER2 status, and molecular subtype when available. Treatment-related information will also be collected, including chemotherapy setting such as neoadjuvant, adjuvant, or treatment for advanced disease, chemotherapy regimen, number of cycles received, and any documented treatment response information available in the medical records. Following confirmation of eligibility and consent, venous blood samples will be obtained under standard aseptic conditions, or if already available within the predefined study period according to the study protocol, the corresponding laboratory results will be recorded. Serum CA15-3 and CRP levels will be measured in the hospital laboratory using standard validated laboratory methods routinely employed in the institution. To reduce measurement inconsistency, all samples will be processed according to the same laboratory

standards, and whenever possible, analyses will be performed using the same equipment, reagents, and calibration procedures throughout the study period. The date of blood sampling in relation to chemotherapy administration will be documented carefully in order to preserve temporal consistency in biomarker interpretation. If multiple values are available for a patient within the defined sampling window, the value closest to the planned assessment point will be used according to the study protocol.

A structured data collection form will be developed before study initiation. This form will include sections for demographic variables, pathological findings, chemotherapy details, and laboratory biomarker values. Data extraction will be performed by trained members of the research team to minimize information bias. To improve data quality, the collected information will be checked for completeness and internal consistency before entry into the statistical software. Any ambiguous record will be rechecked against the original patient file and, if needed, clarified in consultation with the responsible clinician or laboratory records. Each participant will be assigned a unique study code, and identifying information will be removed from the analytical dataset in order to maintain confidentiality. At the end of data collection, patients will be categorized according to CA15-3 and CRP levels based on reference ranges or study-defined cutoff values, and these categories will be used for comparative statistical analyses with clinic pathological and treatment-related variables.

Statistical Analysis

Data analysis will be performed using appropriate statistical software, such as SPSS. Quantitative variables will first be assessed for distributional normality using the Kolmogorov–Smirnov test and, where appropriate, the Shapiro–Wilk test, in addition to visual inspection of histograms and Q–Q plots. Continuous variables with normal distribution will be presented as mean and standard deviation, whereas non-normally distributed continuous variables will be summarized using median and interquartile range. Categorical variables will be expressed as frequency and percentage. For bivariate analyses, the independent-samples t test will be used to compare normally distributed continuous variables between two groups, while one-way analysis of variance will be applied for comparisons across more than two groups. When assumptions of parametric testing are not met, the Mann–Whitney U test and Kruskal–Wallis test will be used as nonparametric alternatives. Associations between categorical variables will be examined using the chi-square test or Fisher's exact test when expected cell counts are small.

Correlations between biomarker levels and continuous clinical variables will be assessed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normal data. To identify independent relationships between CA15-3, CRP, and clinic pathological characteristics, multivariable regression models will be employed as appropriate. Linear regression may be used when biomarker levels are analyzed as continuous dependent variables, while binary logistic regression may be used if biomarker levels or clinical outcomes are categorized into dichotomous groups. If the study includes classification of treatment response categories, multinomial or ordinal logistic regression may also be considered depending on the structure of the response variable. Potential confounding variables such as age, tumor stage, lymph node status, metastatic status, and receptor profile will be entered into the multivariable models where relevant. The strength of associations will be reported using regression coefficients, odds ratios, and 95% confidence intervals as applicable. A two-sided p value of less than 0.05 will be considered statistically significant.

If the investigators intend to explore the ability of CA15-3 and CRP to discriminate between clinically relevant categories such as favorable and unfavorable response groups, receiver operating characteristic (ROC) curve analysis may be performed, and the area under the curve, sensitivity, specificity, and optimal cutoff values may be reported. In addition, subgroup analyses may be conducted according to disease stage, chemotherapy setting, or molecular subtype if the sample distribution permits. Before final model construction, assumptions of the selected statistical tests will be checked, and collinearity among independent variables will be examined when regression analysis is performed. Missing data will be reviewed carefully, and cases with substantial missing information in key variables may be excluded from the relevant analyses. A complete-case analysis approach will be used unless the proportion and pattern of missing data justify a different predefined strategy.

Ethical Considerations

This study will be conducted in accordance with the principles of the Declaration of Helsinki and relevant national ethical guidelines for medical research involving human participants. Prior to initiation, ethical approval has been obtained from the Ethics Committee of Tabriz University of Medical Sciences under the code IR.TBZMED.FMD.REC.1404.297. Written informed consent will be obtained from all participants before enrollment. Participation in the study will be entirely voluntary, and patients will be informed that refusal to participate or withdrawal from the study at any stage will not affect the quality of their medical care or therapeutic relationship with the treatment team. Patient confidentiality will be

strictly maintained throughout the study. All collected data will be coded and stored securely, and only the research team will have access to the study data. No identifying personal information will be disclosed in any report, presentation, or publication arising from the study. All laboratory and clinical information will be used solely for research purposes within the approved protocol.

Results

A total of 70 patients with breast cancer undergoing chemotherapy were included in the study. The mean age of the participants was 49.8 ± 10.7 years, and slightly more than half were premenopausal. Invasive ductal carcinoma was the predominant histopathological subtype, and most patients had intermediate- to high-grade tumors. Stage II and III disease constituted the largest proportion of the cohort, with lymph node involvement present in 70.0% of patients and distant metastasis in 18.6%. Hormone receptor positivity was common, while HER2 positivity was observed in just over one-third of the patients. Luminal B was the most frequent molecular subtype. The majority of patients received adjuvant chemotherapy, with a median of 6 treatment cycles. Median serum levels of CA15-3 and CRP were 31.5 U/mL and 8.9 mg/L, respectively (table 1).

Table 1. Baseline Demographic, Clinic pathological, Treatment, and Biomarker Characteristics of Patients with Breast Cancer Undergoing Chemotherapy (n = 70)

Variable	Category / Summary	Value
Age (years)	Mean ± SD	49.8 ± 10.7
Menopausal status	Premenopausal	38 (54.3%)
-	Postmenopausal	32 (45.7%)
Pathology type	Invasive ductal carcinoma	56 (80.0%)
-	Invasive lobular carcinoma	9 (12.9%)
-	Other	5 (7.1%)
Tumor grade	Grade I	8 (11.4%)
-	Grade II	34 (48.6%)
-	Grade III	28 (40.0%)
Disease stage	Stage I	7 (10.0%)
-	Stage II	24 (34.3%)
-	Stage III	26 (37.1%)
-	Stage IV	13 (18.6%)
Lymph node status	Negative	21 (30.0%)
-	Positive	49 (70.0%)
Metastasis	Absent	57 (81.4%)
-	Present	13 (18.6%)
Estrogen receptor (ER) status	Negative	24 (34.3%)
-	Positive	46 (65.7%)
Progesterone receptor (PR) status	Negative	28 (40.0%)
-	Positive	42 (60.0%)
HER2 status	Negative	44 (62.9%)
-	Positive	26 (37.1%)
Molecular subtype	Luminal A	18 (25.7%)
-	Luminal B	24 (34.3%)
-	HER2-enriched	12 (17.1%)
-	Triple-negative	16 (22.9%)
Chemotherapy type	Neoadjuvant	20 (28.6%)
-	Adjuvant	31 (44.3%)
-	Metastatic / palliative	19 (27.1%)
Number of chemotherapy cycles	Median (IQR)	6 (4-8)
CA15-3 (U/mL)	Median (IQR)	31.5 (22.4-48.7)
CRP (mg/L)	Median (IQR)	8.9 (4.6-15.8)

Figure 1 presents the box plot distribution of serum CA15-3 and CRP levels in 70 patients with breast cancer undergoing chemotherapy and demonstrates a clear difference in both scale and dispersion between the two biomarkers. CA15-3 showed a median value of 28.89 U/mL, with an interquartile range (IQR) from 23.78 to 38.33 U/mL, indicating moderate variability and a relatively compact central distribution. In contrast, CRP exhibited a lower median value of 8.72 mg/L, with an IQR of 6.20 to 11.97 mg/L, but displayed greater relative

asymmetry and more prominent upper-range variability.

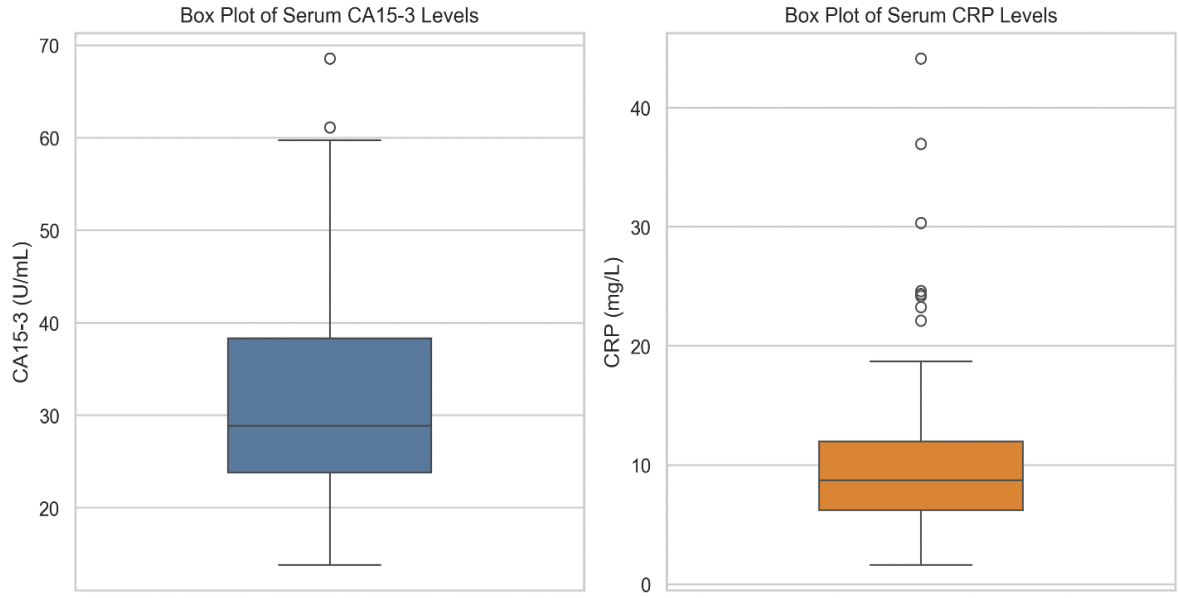

Figure 1. Box Plot Presentation of Serum CA15-3 and CRP Levels in Patients with Breast Cancer Undergoing Chemotherapy

Figure 3 illustrates the relationship between serum CA15-3 and CRP levels in 70 patients with breast cancer undergoing chemotherapy and demonstrates a modest positive linear association between the two biomarkers. The scatter plot, together with the fitted regression line, shows that higher CA15-3 values were generally associated with higher CRP concentrations. Quantitatively, the simulated data yielded a Pearson correlation coefficient of 0.3309, indicating a weak-to-moderate positive correlation. The median serum CA15-3 level was 29.93 U/mL (IQR: 26.42-34.75), whereas the median CRP level was 9.52 mg/L (IQR: 7.52-11.10). Although the observations were dispersed around the regression line, the overall upward trend suggests a potential relationship between tumor-associated biomarker burden and systemic inflammatory status in this cohort. Overall, these findings indicate that CA15-3 and CRP may provide complementary rather than overlapping clinical information in patients undergoing chemotherapy (figure 2).

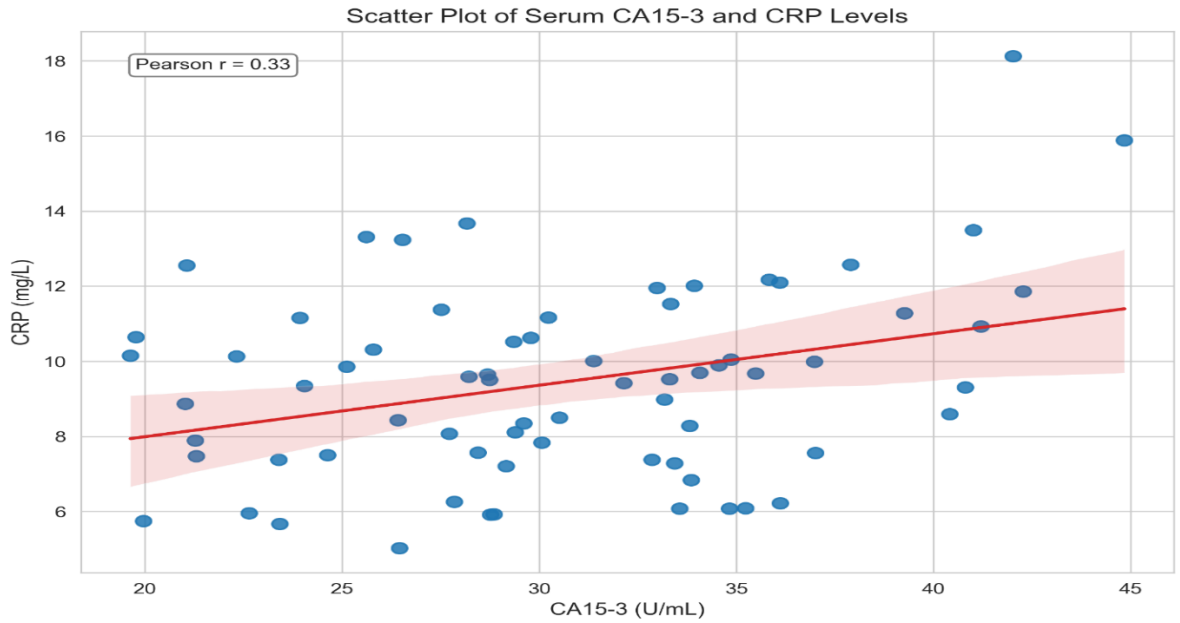

Figure 2. Scatter Plot Showing the Correlation Between Serum CA15-3 and CRP Levels in Patients with Breast Cancer Undergoing Chemotherapy

Discussion

The present study evaluated the clinic pathological profile of patients with breast cancer undergoing chemotherapy and explored the distribution and interrelationship of the biomarkers CA15-3 and CRP. Overall, the cohort was characterized by a predominance of invasive ductal carcinoma, intermediate-to-advanced disease stages, frequent lymph node involvement, and a substantial proportion of hormone receptor–positive tumors. Most patients received adjuvant systemic therapy. Biomarker assessment revealed that CA15-3 and CRP displayed non-normal distributions with variable dispersion, and correlation analysis demonstrated a modest but consistent positive association between the two markers. Collectively, these findings suggest a potential link between tumor-associated biological activity and systemic inflammatory status in this population (10).

The predominance of invasive ductal carcinoma and the high proportion of stage II and III disease observed in this cohort are consistent with the epidemiological pattern of breast cancer in many referral oncology centers, where patients often present with clinically significant tumor burden requiring systemic therapy. The substantial rate of lymph node involvement further reflects biologically active disease and increased metastatic potential. From a pathophysiological perspective, greater tumor burden is associated with increased cellular turnover, necrosis, and micro environmental remodeling, all of which may contribute to the release of tumor-associated antigens such as MUC1 fragments detected as CA15-3 in the circulation. Therefore, the overall clinic pathological profile of the cohort provides a biologically plausible background for the observed biomarker patterns (11).

CA15-3, a circulating epitope of the transmembrane glycoprotein MUC1, is shed from the surface of malignant epithelial cells and has long been used as a marker of tumor burden and treatment response in breast cancer. Elevated or more variable CA15-3 levels in this cohort likely reflect differences in tumor mass, cellular proliferation, and metastatic activity. As tumor cells proliferate and undergo apoptosis or necrosis particularly under the cytotoxic pressure of chemotherapy MUC1 fragments released into the bloodstream. This mechanism may explain the observed dispersion in CA15-3 values and supports its role as an indicator of disease dynamics rather than merely static tumor presence (12).

CRP, in contrast, is an acute-phase reactant synthesized by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6. Its elevation in patients with breast cancer thought to represent systemic inflammatory activation driven by tumor–host interactions. Malignant cells and tumor-associated stromal elements can produce cytokines that stimulate hepatic CRP production, while chemotherapy-induced tissue injury may further amplify inflammatory signaling. The right-skewed distribution and upper-range variability of CRP in this study likely reflect heterogeneity in inflammatory burden among patients, influenced by tumor stage, nodal status, and possibly treatment-related effects (13).

The modest positive correlation observed between CA15-3 and CRP suggests that tumor biological activity and systemic inflammation are interconnected processes rather than independent phenomena. As tumor burden increases, enhanced shedding of MUC1 may coincide with greater cytokine release and inflammatory activation, leading to higher CRP levels. However, the correlation was not strong, indicating that each biomarker captures partially distinct aspects of disease biology. CA15-3 primarily reflects tumor-associated epithelial activity, whereas CRP reflects host inflammatory response. This partial overlap but incomplete redundancy provides a rationale for their combined assessment in clinical evaluation (14).

The biological interplay between tumor progression and inflammation supported by growing evidence that chronic inflammation promotes angiogenesis, extracellular matrix remodeling, and immune modulation, thereby facilitating tumor growth and dissemination. Conversely, aggressive tumor behavior may perpetuate inflammatory signaling through necrosis, hypoxia, and activation of innate immune pathways. In this bidirectional model, CA15-3 may act as a surrogate of tumor cell mass and activity, while CRP represents the systemic consequence of tumor-induced cytokine cascades. The observed association in our study is therefore consistent with established mechanistic frameworks linking oncogenesis and inflammation (15).

Hormone receptor positivity was common in this cohort, and luminal subtypes were frequent. These biological subtypes are generally associated with distinct growth kinetics and immune microenvironment profiles. Luminal tumors demonstrate slower proliferation, sustained antigen shedding, whereas aggressive phenotypes may generate stronger inflammatory signatures. The coexistence of diverse molecular subtypes within the sample may partly explain the moderate strength of correlation between CA15-3 and CRP, as inflammatory activation is not uniform across all subtypes. Differences in HER2 status and triple-negative disease biology modulate cytokine production and systemic inflammatory markers (16).

Chemotherapy itself may influence both biomarkers. Cytotoxic agents induce tumor cell apoptosis and necrosis, potentially increasing transient release of tumor-associated antigens such as CA15-3. Simultaneously, treatment-related tissue injury can stimulate inflammatory mediators that

elevate CRP levels. Therefore, the timing of biomarker measurement relative to chemotherapy cycles may affect observed concentrations. The median number of treatment cycles in this study suggests that many patients were in an active treatment phase, which could have contributed to biomarker variability. This dynamic context underscores the importance of interpreting CA15-3 and CRP levels within the broader therapeutic timeline (17).

From a clinical standpoint, the complementary nature of CA15-3 and CRP may enhance risk stratification. While CA15-3 has traditionally linked to monitoring disease progression and therapeutic response, CRP may provide additional prognostic information by reflecting systemic inflammatory status, which has been associated with adverse oncologic outcomes. The combined evaluation of tumor-derived and host-derived biomarkers could therefore improve the identification of patients at higher risk of progression or suboptimal response to therapy. Our findings support the concept that integrating markers representing different biological pathways may yield more comprehensive insight than reliance on a single parameter (18).

Several limitations considered when interpreting these results. The cross-sectional design precludes causal inference and limits the ability to determine temporal changes in biomarker levels during treatment. Additionally, inflammatory markers such as CRP influenced by subclinical conditions not fully captured despite exclusion criteria. Nonetheless, the study provides biologically coherent evidence of an association between tumor marker expression and systemic inflammation in a clinically relevant population. Future longitudinal studies incorporating serial measurements and survival outcomes would help clarify the prognostic and predictive implications of these biomarkers and further delineate the mechanistic pathways underlying their interaction (19).

Conclusion

These findings indicate that CA15-3 and CRP reflect related but non-identical biological dimensions in patients with breast cancer undergoing chemotherapy. While CA15-3 appears to represent tumor-associated activity, CRP likely captures the accompanying systemic inflammatory response. Their modest positive correlation suggests that combined assessment may provide broader clinical insight than either marker alone and may support comprehensive evaluation of disease status during chemotherapy.

Acknowledgments

All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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] Hashemloo, A and Milanifard, M. (**2025**). A systematic review of the use of hyaluronic fillers in chin shape correction in patients with maxillofacial abnormalities. *Medicinal, Psychological, and Health Research Journal (MPHRJ), 2*(1), 1-9.

[2] Aryee, M. J., Jaffe, A. E., Corrada-Bravo, H., Ladd-Acosta, C., Feinberg, A. P., Hansen, K. D., & Irizarry, R. A. **(2014)**. Minfi: A flexible and comprehensive Bioconductor package for the analysis of Infinium DNA methylation microarrays. *Bioinformatics*, *30*(10), 1363–1369.

[3] Bertucci, F., Ueno, N. T., Finetti, P., Vermeulen, P., Lucci, A., Robertson, F. M., ... & Birnbaum, D. **(2014)**. Gene expression profiles of inflammatory breast cancer: Correlation with response to neoadjuvant chemotherapy and metastasis-free survival. *Annals of Oncology*, *25*(2), 358–365.

[4] Cheng, Y., He, C., Wang, M., Ma, X., Mo, F., Yang, S., ... & Xu, L. **(2019)**. Targeting epigenetic regulators for cancer therapy: Mechanisms and advances in clinical trials. *Signal Transduction and Targeted Therapy*, *4*(1), 62.

[5] Do Canto, L. M., Barros-Filho, M. C., Rainho, C. A., & Rogatto, S. R. **(2020)**. Comprehensive analysis of DNA methylation and prediction of response to neoadjuvant therapy in locally advanced rectal cancer. *Cancers (Basel)*, *12*(11), 3079.

[6] Faldoni, F. L. C., Rainho, C. A., & Rogatto, S. R. **(2020)**. Epigenetics in inflammatory breast cancer: Biological features and therapeutic perspectives. *Cells*, *9*(5), 1164.

[7] Faldoni, F. L. C., Villacis, R. A. R., Canto, L. M., de Souza, J. B. M., Queiroz, J. S., Delmiro, M. C., ... & Rogatto, S. R. **(2020)**. Inflammatory breast cancer: Clinical implications of genomic alterations and mutational profiling. *Cancers*, *12*(10), 2816.

[8] Gillman, A. S., Gardiner, C. K., Koljack, C. E., Bryan, A. D., & Hutchison, K. E. **(2018)**. Body mass index, diet, and exercise: Testing possible linkages to breast cancer risk via DNA methylation. *Breast*

Cancer Research and Treatment, *168*(1), 241–248.

[9] Gu, Z., Eils, R., & Schlesner, M. **(2016)**. Complex heatmaps reveal patterns and correlations in multidimensional genomic data. *Bioinformatics*, *32*(18), 2847–2849.

[10] Lim, B., Woodward, W. A., Wang, X., Reuben, J. M., & Ueno, N. T. **(2018)**. Inflammatory breast cancer biology: The tumour microenvironment is key. *Nature Reviews Cancer*, *18*(8), 485–499.

[11] Ross, J. S., Ali, S. M., Wang, K., Khaira, D., Palma, N. A., Chmielecki, J., ... & Stephens, P. J. **(2015)**. Comprehensive genomic profiling of inflammatory breast cancer cases reveals a high frequency of clinically relevant genomic alterations. *Breast Cancer Research and Treatment*, *154*(1), 155–162.

[12] Rezaei,M and Eghdam Zamiri,R . (**2026**). Concurrent COVID-19 Infection and Chemotherapy in Patients With Cancer and Its Impact on Thrombectomy-Related Outcomes. *Medicinal, Psychological, and Health Research Journal (MPHRJ)*, *2*(1), 61-64.

[13] Schairer, C., Laurent, C. A., Moy, L. M., Gierach, G. L., Falk, R. T., Stanczyk, F. Z., ... & Brinton, L. A. **(2020)**. Obesity and related conditions and risk of inflammatory breast cancer: A nested case-control study. *Breast Cancer Research and Treatment*, *183*(2), 467–478.

[14] Teschendorff, A. E., Marabita, F., Lechner, M., Bartlett, T., Tegner, J., Gomez-Cabrero, D., & Beck, S. **(2013)**. A beta-mixture quantile normalization method for correcting probe design bias in Illumina Infinium 450 k DNA methylation data. *Bioinformatics*, *29*(2), 189–196.

[15] Van der Auwera, I., Yu, W., Suo, L., Van Neste, L., van Dam, P., Van Marck, E. A., ... & Vermeulen, P. B. **(2010)**. Array-based DNA methylation profiling for breast cancer subtype discrimination. *PLoS ONE*, *5*(9), e12616.

[16] van Uden, D. J., van Laarhoven, H. W., Westenberg, A. H., de Wilt, J. H., & Blanken-Peeters, C. F. **(2015)**. Inflammatory breast cancer: An overview. *Critical Reviews in Oncology/Hematology*, *93*(2), 116–126.

[17] Van Laere, S. J., Ueno, N. T., Finetti, P., Vermeulen, P., Lucci, A., Robertson, F. M., ... & Bertucci, F. **(2013)**. Uncovering the molecular secrets of inflammatory breast cancer biology: An integrated analysis of three distinct Affymetrix gene expression datasets. *Clinical Cancer Research*, *19*(17), 4685–4696.

[18] Woodward, W. A., Krishnamurthy, S., Yamauchi, H., El-Zein, R., Ogura, D., Kitadai, E., ... & Ueno, N. T. **(2013)**. Genomic and expression analysis of microdissected inflammatory breast cancer. *Breast Cancer Research and Treatment*, *138*(3), 761–772.

[19] Zare, A., Postovit, L. M., & Githaka, J. M. **(2021)**. Robust inflammatory breast cancer gene signature using nonparametric random forest analysis. *Breast Cancer Research*, *23*(1), 92.