RESEARCH ARTICLE

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Temporal Hematologic Alterations in Women Receiving Pharmacotherapy for Breast Cancer: A Prospective Analysis

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Abstract

Background: Breast cancer pharmacotherapy commonly results in hematologic toxicity and systemic inflammatory shifts that may compromise treatment tolerance. This study evaluated baseline hematologic characteristics and early hematologic changes following pharmacotherapy among patients treated in second-referral centers in Indonesia. **Methods:** This prospective cohort study enrolled 106 women with confirmed breast cancer between January and October 2025. Hematologic evaluations were performed before treatment and at Weeks 1 and 3. Assessed parameters included hemoglobin, leukocyte and platelet counts, differential counts, the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), monocyte–lymphocyte ratio (MLR), and the pan-immune-inflammation value (PIV). Friedman's two-way analysis of variance by ranks was used for pre–post comparisons. Subgroup comparisons between survivors and non-survivors used Mann–Whitney U tests. **Results:** The mean age was 51.9 ± 9.7 years, with most patients presenting with locally advanced disease (58.5%) and invasive ductal carcinoma (84%). Baseline hemoglobin averaged 11.9 g/dL and leukocyte count 7.5 × 10^3/μL. Marked hematologic suppression occurred after therapy: leukocyte and absolute neutrophil counts declined significantly at week 1 with partial recovery by week 3 ($p < 0.001$). Inflammatory indices showed substantial fluctuations, with significant changes in PLR, MLR, and PIV (all $p < 0.001$). Anemia increased from 51.9% at baseline to 74.0% post-therapy. Neutropenia occurred in 1.9% at baseline, 41.7% at week 1, and 1.1% at week 3. Among survival subgroups, only MLR differed significantly ($p = 0.043$). **Conclusion:** The mean age was 51.9 ± 9.7 years, with most patients presenting with locally advanced disease (58.5%) and invasive ductal carcinoma (84%). Baseline hemoglobin averaged 11.9 g/dL and leukocyte count 7.5 × 10^3/μL. Marked hematologic suppression occurred after therapy: leukocyte and absolute neutrophil counts declined significantly at week 1 with partial recovery by week 3 ($p < 0.001$). Inflammatory indices showed substantial fluctuations, with significant changes in PLR, MLR, and PIV (all $p < 0.001$). Anemia increased from 51.9% at baseline to 74.0% post-therapy. Neutropenia occurred in 1.9% at baseline, 41.7% at week 1, and 1.1% at week 3. Among survival subgroups, only MLR differed significantly ($p = 0.043$).

Keywords: breast neoplasms- antineoplastic agents- hematologic toxicity- neutropenia- inflammation mediators

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Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and continues to impose a major clinical and economic burden despite substantial therapeutic advances [1]. Systemic pharmacotherapyincluding cytotoxic chemotherapy, targeted therapies, and endocrine agentsconstitutes a fundamental component of treatment across disease stages [2]. However, these therapies exert wide-ranging effects on hematopoiesis and systemic inflammation, leading to predictable yet clinically significant hematologic toxicities [3, 4]. Myelosuppression, particularly neutropenia, is among the most important dose-limiting toxicities and is associated with increased risk of febrile neutropenia, treatment delays, dose reductions, infection-related morbidity, and mortality [5]. The early phase of treatment, especially the first cycle, is a critical window during which hematologic nadirs occur and during which careful monitoring can meaningfully influence clinical decision-

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making [6]. Beyond absolute cell counts, systemic inflammatory indices derived from routine hematologic parameters such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and pan-immune-inflammation value (PIV) have emerged as potential biomarkers reflecting host inflammatory state, tumor–immune interactions, and treatment tolerance [7, 8]. These markers have been associated with prognosis across multiple malignancies, including breast cancer. However, most studies focus on their pre-treatment prognostic value rather than examining how these indices fluctuate during the earliest treatment intervals. Detailed characterization of these short-term hematologic and inflammatory dynamics may provide insight into early marrow stress, immune perturbation, and the physiologic cost of therapy. Such information may have particular value in identifying patients at elevated risk of toxicity, optimizing supportive care strategies, and enhancing individualized treatment planning.

Nevertheless, despite growing interest, there remains a lack of high-quality prospective data describing temporal changes in hematologic parameters and inflammatory indices across the initial weeks of pharmacotherapy. This includes understanding the magnitude of early hematologic suppression, identifying which indices exhibit predictable versus variable trajectories, and determining whether early inflammatory shifts carry prognostic significance. Addressing these knowledge gaps is essential, as early toxicities often shape the feasibility of continuing full-dose therapy and may influence downstream outcomes. Therefore, this study aimed to provide a comprehensive evaluation of early hematologic and inflammatory changes following systemic pharmacotherapy in breast cancer patients. The specific objectives were to characterize baseline hematologic profiles prior to treatment initiation; describe short-term temporal changes in hematologic counts and inflammatory indices at one and three weeks following pharmacotherapy; assess the frequency and severity of treatment-emergent anemia, leukopenia, neutropenia, and thrombocytopenia; and explore whether baseline hematologic or inflammatory markers differ between survivors and non-survivors, thereby identifying potential early prognostic indicators. By delineating these trajectories in detail, this study aims to advance understanding of early treatment-associated hematologic dynamics and to inform supportive care strategies that promote treatment continuity and safety.

Materials and Methods

Study design

This study employed a prospective cohort design at two secondary referral centers in East Java, Indonesia, to evaluate early hematologic and inflammatory changes following systemic pharmacotherapy in breast cancer patients. Data collection occurred over a 10-month period, from January to October 2025. All participants were treated in second-referral hospitals that provide comprehensive oncologic care, including cytotoxic chemotherapy, targeted therapy, and endocrine therapy. The study was designed to capture real-world clinical practice, including heterogeneity in treatment regimens and patient characteristics. Ethical approvals were obtained from the institutional review boards of both participating hospitals (197/KEP/2024 from Universitas Airlangga Hospital and 445/02/KOM.ETIK/2025 from Haji General Hospital), and all participants provided written informed consent [9].

Study population and sampling

A total of 106 women with confirmed breast cancer through triple assessments (clinical, imaging, and pathology) were enrolled consecutively. Consecutive total sampling was chosen to ensure that all eligible patients initiating systemic pharmacotherapy during the study period were included, minimizing selection bias and maximizing representativeness within the treatment-setting context. Patients were enrolled at the time of treatment planning or immediately prior to the first cycle of systemic pharmacotherapy.

Inclusion and exclusion criteria

Eligible participants were adult women aged 18 years or older with a confirmed diagnosis of breast cancer (all stages) for whom systemic pharmacotherapy was planned (Figure 1). Patients were required to have available baseline laboratory tests and be medically stable for treatment initiation. Exclusion criteria included known other malignancies, pre-existing severe bone marrow disorders, active uncontrolled infections at baseline, recent blood transfusion or granulocyte colony-stimulating factor administration before initial sampling, or incomplete follow-up laboratory data at key time points. Patients receiving concurrent investigational agents or undergoing neoadjuvant radiotherapy were also excluded to prevent confounding effects on hematologic parameters.

Data collection procedures

Demographic, clinical, and oncologic data including age, comorbidities, tumor stage, histopathology, and immunohistochemical subtype were collected from medical records at baseline. Pharmacotherapy regimens were documented in detail, including drug combinations, treatment intent (neoadjuvant, adjuvant, or palliative), and cycle timing. Data collection was standardized using a predefined case report form to ensure consistency across investigators. Of note, the study focused on routine hematologic parameters collected at predefined time points. Systematic documentation of supportive care interventions including prophylactic or therapeutic granulocyte colony-stimulating factor (G-CSF), red blood cell or platelet transfusions, and antibiotic administration was not uniformly available across participating centers. In addition, body temperature was not systematically monitored during the neutropenic period; therefore, febrile neutropenia was not assessed as a study endpoint.

Hematologic and inflammatory assessment

Hematologic indices were measured at three predetermined time points: (1) baseline (pre-pharmacotherapy), (2) week 1 after treatment initiation, and (3) week 3 after initiation, corresponding to expected hematologic nadirs and early recovery phases. Parameters

assessed included hemoglobin, total leukocyte count, platelet count, differential leukocyte counts, absolute neutrophil count (ANC), and absolute lymphocyte and monocyte counts. Inflammatory composite indicesNLR, PLR, MLR, and PIVwere calculated using established formulas.

Outcome measures

Primary outcomes were the magnitude and direction of change in hematologic and inflammatory indices at week 1 and week 3. Secondary outcomes included the incidence and severity of anemia, neutropenia, leukopenia, and thrombocytopenia, classified according to standard hematologic thresholds. An exploratory outcome compared baseline hematologic and inflammatory markers between survivors and non-survivors during the study period to identify potential early prognostic indicators.

Statistical analysis

Data analysis was conducted using appropriate parametric or non-parametric methods based on distribution. Continuous variables were assessed for normality using the Shapiro–Wilk test. For within-subject comparisons across multiple time points, Friedman's two-way analysis of variance by ranks was applied for non-normally distributed variables. Categorical variables, including anemia and neutropenia frequencies, were summarized as proportions. Comparisons between survivor and non-survivor groups were performed using the Mann–Whitney U test due to the small sample size in the non-survivor group. A two-tailed p-value <0.05 was considered statistically significant.

Results

Baseline demographic characteristics

A total of 106 women were included in the study, all of whom were female (100%). The mean age of the cohort was 51.92 ± 9.7 years, reflecting a predominantly mid-to-late adulthood population (Table 1). Age distribution analysis showed that no patients were younger than 30 years. The largest age groups were those aged 51–60 years (37.7%) and 41–50 years (34.0%). Smaller proportions were observed in the 31–40 years (9.4%), 61–70 years (15.1%), 71–80 years (2.8%), and over 80 years (0.9%) categories, indicating that most patients presented during the typical peri- and post-menopausal years. Educational background varied across the cohort. Approximately one-third had completed high school (33.0%), while a slightly larger proportion held higher education or university degrees (36.8%). Elementary education was reported in 20.8% of patients, and 7.5% had completed secondary school. Only 1.9% had no formal education. In terms of employment status, two-thirds of patients were unemployed (66.0%), whereas the remaining 34.0% were employed at the time of diagnosis and treatment initiation. Most participants were married (85.8%), while 7.5% were single and 6.6% were widowed.

Comorbid conditions were present in 59.4% of the cohort, whereas 40.6% reported no known comorbidities.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort

Parameter	N = 106
Sex (n; %)	
Female	106 (100.0%)
Age in years (mean ± SD)	51.92 ± 9.7
Age Range (n; %)	
≤30 years	0 (0.0%)
31-40 years	10 (9.4%)
41-50 years	36 (34.0%)
51-60 years	40 (37.7%)
61-70 years	16 (15.1%)
71-80 years	3 (2.8%)
>80 years	1 (0.9%)
Education (n; %)	
No formal education	2 (1.9%)
Elementary	22 (20.8%)
Secondary	8 (7.5%)
High School	35 (33.0%)
Higher education / University	39 (36.8%)
Employment Status (n; %)	
Unemployed	70 (66.0%)
Employed	36 (34.0%)
Marital Status (n; %)	
Single	8 (7.5%)
Married	91 (85.8%)
Widow	7 (6.6%)
Comorbidities (n; %)	
No	43 (40.6%)
Yes	63 (59.4%)
Hypertension (n)	32
Diabetes mellitus (n)	12
Cardiovascular diseases (n)	16
Pulmonary diseases (n)	7
Miscellaneous (n)	37
History of Breast Cancer Treatment (n; %)	
No	32 (30.2%)
Yes	74 (69.8%)
Surgery (n)	60
Pharmacotherapy (n)	49
Radiotherapy (n)	4

Among those with comorbidities, hypertension was the most common (n = 32), followed by cardiovascular diseases (n = 16) and diabetes mellitus (n = 12). Pulmonary diseases were documented in 7 patients. Additionally, 37 patients had miscellaneous comorbidities that did not fall into the predefined categories. Overall, the data show that a substantial proportion of patients presented with at least one chronic medical condition prior to pharmacotherapy initiation. Prior therapeutic exposure varied among participants. A total of 74 patients (69.8%) had undergone at least one form of previous breast cancer

Table 2. Breast Cancer Profile of the Study Cohort

Parameter	N = 106
Breast Cancer Stage (n; %)	
Early	14 (13.2%)
Locally advanced	62 (58.5%)
Metastatic	30 (28.3%)
Metastasis Site (n)	
Brain	1
Lung / Pleura	16
Liver	9
Bone	10
Tissue Histopathology (n; %)	
Invasive ductal carcinoma (IDC)	89 (84.0%)
Invasive lobular carcinoma (ILC)	5 (4.7%)
Mixed IDC/ILC	8 (7.5%)
Miscellaneous (e.g., mucinous)	1 (0.9%)
Unknown	3 (2.8%)
Tumor Grade (n; %)	
Grade I	10 (9.4%)
Grade II	38 (35.8%)
Grade III	43 (40.6%)
Unknown	15 (14.2%)
Immunohistochemistry (n; %)	
Luminal A	10 (9.4%)
Luminal B HER2-	28 (26.4%)
Luminal B HER2+	20 (18.9%)
HER2 enriched	16 (15.1%)
HER2 low	7 (6.6%)
TNBC	8 (7.6%)
Unknown	17 (16.0%)
Pharmacotherapy Status (n; %)	
Neoadjuvant	36 (34.0%)
Adjuvant	40 (37.7%)
Palliative	30 (28.3%)
Pharmacotherapy (n)	
Paclitaxel – Carboplatin	8
Docetaxel – Carboplatin	20
Docetaxel – Cyclophosphamide	4
Doxorubicin – Cyclophosphamide	17
Docetaxel – Doxorubicin – Cyclophosphamide	12
Docetaxel – Epirubicin – Cyclophosphamide	5
Epirubicin – Paclitaxel	1
Epirubicin – Docetaxel	1
Epirubicin – Carboplatin	3
Epirubicin – Cyclophosphamide – 5FU	3
Cyclophosphamide – Methotrexate – 5FU	1
Paclitaxel – Trastuzumab	2
Docetaxel – Trastuzumab	2
Paclitaxel – Carboplatin – Trastuzumab	2
Docetaxel – Carboplatin – Trastuzumab	11
Epirubicin – Docetaxel – Trastuzumab	1
Trastuzumab	2
Pharmacotherapy (n)	
Carboplatin – Gemcitabine	1
Paclitaxel – Gemcitabine	1
Docetaxel – Capecitabine	1
Vinorelbine	3
Eribulin	1
Leuprorelin	1
Tamoxifen	2
Fulvestrant	1
Letrozole	3
Goserelin	7
Bevacizumab	2
Zolendronic acid	5

* The data were not normally distributed based on the Shapiro–Wilk test (N < 100); therefore, values are presented as median [IQR]

treatment, whereas 32 patients (30.2%) were treatment-naïve at baseline. Among those with prior treatment, surgery was the most common modality (n = 60), followed by pharmacotherapy (n = 49). A smaller number had received radiotherapy (n = 4). These data demonstrate considerable variability in treatment history before the current evaluation.

Breast cancer profile of the study cohort

Among the 106 patients, the majority presented with locally advanced breast cancer (58.5%). Early-stage disease accounted for 13.2% of cases, while 28.3% had metastatic disease at the time of assessment (Table 2). Among patients with metastasis, the most common metastatic sites were the lung or pleura (n = 16), followed by bone (n = 10) and liver (n = 9). Brain metastasis was documented in one patient. Invasive ductal carcinoma (IDC) was the predominant histopathologic subtype, identified in 84.0% of patients. Invasive lobular carcinoma (ILC) was uncommon, totaling 4.7%, while mixed IDC/ILC histology was observed in 7.5%. A small number of tumors fell into miscellaneous categories such as mucinous carcinoma (0.9%). Histopathologic subtype was not documented in 2.8% of cases. Tumor grading revealed that 9.4% of tumors were classified as Grade I and 35.8% as Grade II. High-grade disease (Grade III) constituted 40.6% of the cohort, while grade information was unavailable for 14.2% of patients. Overall, intermediate-to-high-grade tumors made up the majority of documented cases. Immunohistochemical subtyping demonstrated notable heterogeneity. Luminal B HER2-negative tumors were the most frequent subtype (26.4%), followed by Luminal B HER2-positive (18.9%) and HER2-enriched (15.1%). Luminal A was less common at 9.4%. HER2-low expression was recorded in 6.6% of patients. Triple-negative breast cancer (TNBC) accounted for 7.6%. Immunohistochemistry data were unavailable for 16.0% of the cohort.

At the time of evaluation, patients were receiving systemic therapy for varying clinical intents. Neoadjuvant

treatment accounted for 34.0% of cases, adjuvant therapy for 37.7%, and palliative therapy for 28.3%. These proportions reflect a mixture of patients across the disease continuum, from potentially curative to supportive care contexts. A wide variety of systemic regimens were also administered. The most frequently prescribed combinations included docetaxel–carboplatin (n = 20), doxorubicin–cyclophosphamide (n = 17), and docetaxel–doxorubicin–cyclophosphamide (n = 12). Several less common regimens were also used, including multiple epirubicin-based combinations, hormonal therapies such as tamoxifen (n = 3), letrozole (n = 7), and fulvestrant (n = 2), and supportive agents such as zoledronic acid (n = 5). HER2-targeted combinations (e.g., paclitaxel–carboplatin–trastuzumab; docetaxel–trastuzumab) were used in small numbers. Overall, the pharmacotherapy patterns reflect substantial regimen diversity in alignment with individualized clinical indications.

Baseline hematological profile prior to pharmacotherapy

Baseline hematologic assessments were available for all 106 patients prior to the initiation of systemic treatment (Table 3). The mean hemoglobin level for the cohort was 11.9 ± 1.3 g/dL, indicating that many patients began therapy with values near the lower threshold of the normal range. Platelet counts demonstrated a median value of 307.0 × 10^3/μL [IQR: 237.5–367.8], reflecting considerable interindividual variability but generally preserved thrombopoietic function at baseline. Total leukocyte counts exhibited a mean of 7.5 ± 2.6 × 10^3/μL, consistent with broad normal-range distribution across the cohort. Differential leukocyte analysis showed a median neutrophil percentage of 65.5% [58.8–72.0], a lymphocyte percentage of 24.8% [18.8–30.8], and a monocyte percentage of 7.1% [5.7–8.8], based on available data from 102–105 patients. The corresponding median ANC was 4.6 × 10^3/μL [3.4–6.3], indicating adequate neutrophil reserves prior to treatment. Inflammatory composite indices derived from baseline hematologic parameters showed moderate variability. NLR demonstrated a median value of 2.7 [2.0–3.8], while PLR had a median of 163.2 [131.5–253.8]. MLR exhibited a relatively narrow distribution, with a median of 0.3 [0.2–0.4]. PIV, a more complex measure incorporating neutrophil, platelet, monocyte, and lymphocyte parameters, had a median value of 386.8 [202.9–649.6], reflecting broader dispersion across patients.

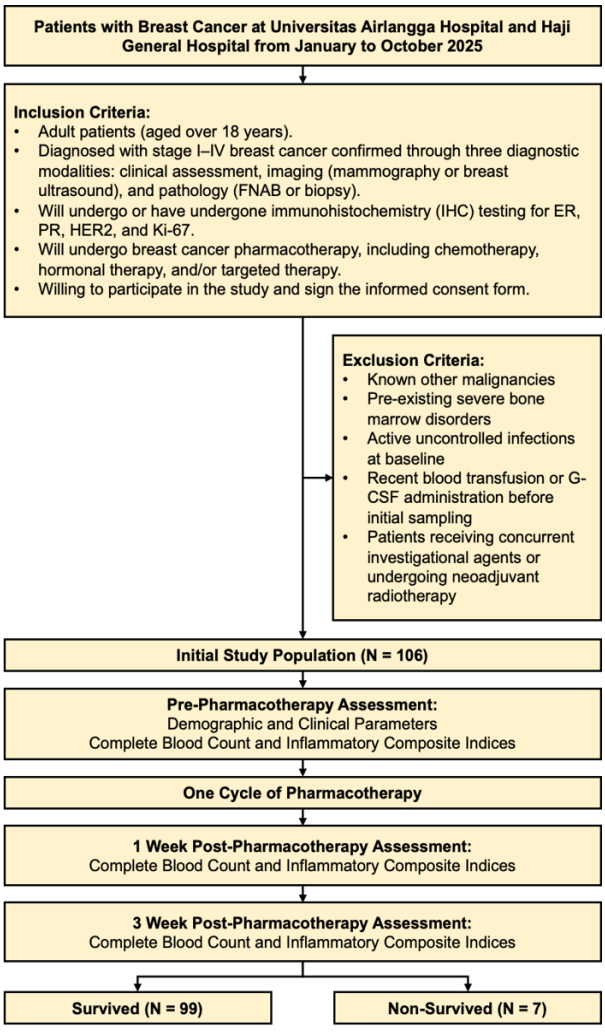

Figure 1. Flowchart of Study Design

Comparison of hematological profiles before and after pharmacotherapy

Hematologic parameters were evaluated longitudinally in a subset of patients with complete data at all three time points (pre-treatment, week 1, and week 3; Table 4). A total of 57 patients contributed paired hemoglobin, platelet count, and total leukocyte data to this analysis. Median hemoglobin at baseline was 11.7 g/dL [10.8–12.4]. At week 1 following pharmacotherapy initiation, hemoglobin showed a slight numerical increase to 11.9 g/dL [10.7–12.7]. By week 3, hemoglobin levels had decreased to 11.2 g/dL [10.2–11.9]. Overall, the temporal differences were statistically significant ($p < 0.001$), indicating measurable variation across the three time points. Baseline platelet

Table 3. Baseline Hematological Profile Prior to Pharmacotherapy

Parameter	Central Tendency
Hemoglobin Level (g/dL) (N = 106)	11.9 ± 1.3
Platelet Count (x10^3 cells/μL) (N = 106)	307.0 [237.5 – 367.8]*
WBC Count (x10^3 cells/μL) (N = 106)	7.5 ± 2.6
Differential Count	
Neutrophil (%) (N = 105)	65.5 [58.8 – 72.0]*
Lymphocyte (%) (N = 102)	24.8 [18.8 – 30.8]*
Monocyte (%) (N = 102)	7.1 [5.7 – 8.8]*
Absolute Neutrophil Count (x10^3 cell/μL) (N = 105)	4.6 [3.4 – 6.3]*
Neutrophil-Lymphocyte Ratio (NLR) (N = 102)	2.7 [2.0 – 3.8]*
Platelet-Lymphocyte Ratio (PLR) (N = 102)	163.2 [131.5 – 253.8]*
Monocyte-Lymphocyte Ratio (MLR) (N = 102)	0.3 [0.2 – 0.4]*
Pan-immune-inflammation value (PIV) (N = 102)	386.8 [202.9 – 649.6]*

* The data were not normally distributed according to the Shapiro–Wilk test (N < 100); therefore, the results are presented as median [IQR]

count demonstrated a median value of 324.0 × 10^3/μL [264.5–399.5]. At week 1, platelet counts decreased to 290.0 × 10^3/μL [205.0–349.5], followed by an increase at week 3 to 354.0 × 10^3/μL [257.0–433.0]. These differences reached statistical significance (p <0.001). The observed fluctuations reflect distinct early-cycle platelet dynamics following pharmacotherapy administration. Total leukocyte counts declined substantially from a baseline median of 7.4 × 10^3/μL [5.7–9.9] to 3.6 × 10^3/μL [2.0–5.6] at week 1. By week 3, counts rose toward baseline values, reaching 6.9 × 10^3/μL [5.2–10.1]. This pattern resulted in highly significant differences across time points (p <0.001). Differential leukocyte percentages also exhibited significant changes. Neutrophil percentages were relatively stable (baseline 65.5% [59.3–73.3], week 1: 64.6% [29.4–76.8], week 3: 67.9% [59.5–75.2]; p = 0.330). In contrast, lymphocyte percentages increased at week 1 (29.9% [20.5–55.1]) compared to baseline (23.7% [18.3–30.2]) and subsequently declined at week 3 (21.6% [15.5–28.2]), producing a statistically significant difference (p <0.001). Monocyte percentages decreased sharply at week 1 (1.8% [0.8–6.4]) compared to baseline (7.2% [5.3–8.4]) and increased again by week 3 (8.5% [7.1–10.9]), with statistically significant differences overall (p <0.001). Consistent with total leukocyte patterns, ANC declined from 4.7 × 10^3/μL [3.5–6.9] at baseline to 2.6 × 10^3/μL [0.7–4.4] at week 1, followed by recovery to 4.9 × 10^3/μL [3.2–7.0] at week 3. These changes were statistically significant (p <0.001).

All calculated inflammatory indices showed significant alterations over time. NLR decreased from 2.7 [2.0–3.9] at baseline to 2.1 [0.5–3.8] at week 1, then increased to 3.1 [2.1–5.0] at week 3 (p = 0.003). PLR increased markedly at week 1 (274.2 [200.1–343.4]) from baseline (177.6 [135.7–282.0]), followed by a decline to 236.0 [163.0–286.2] at week 3 (p <0.001). MLR decreased sharply from 0.3 [0.2–0.4] at baseline to 0.1 [0.0–0.2] at week 1 and subsequently rose to 0.4 [0.3–0.6] at week 3 (p <0.001). PIV demonstrated the most pronounced change, declining from 418.0 [209.3–711.5] at baseline to 31.5 [9.9–87.2] at week 1, then increasing substantially to 534.2 [354.6–1467.7] at week 3 (p <0.001). Finally, the prevalence of anemia increased from 51.9% at baseline (55/106) to 55.7% at week 1 (34/61) and further to 74.0% at week 3 (71/96). Neutropenia was rare at baseline (1.9%, 2/105) but increased markedly at week 1 (41.7%, 25/60), predominantly moderate to severe, then decreased to 1.1% at week 3 (1/94). Of note, neutropenia was defined based on laboratory absolute neutrophil count thresholds. Febrile neutropenia could not be evaluated because temperature monitoring during the neutropenic interval was not systematically performed. Meanwhile, thrombocytopenia increased from 1.9% at baseline to 6.6% at week 1 and was observed in 5.2% of available samples at week 3.

Table 4. Comparison of Hematological Profiles Before and After Pharmacotherapy

Parameter	Pre-pharmacotherapy	Post-Pharmacotherapy Week-1	Post-Pharmacotherapy Week-3	p-value#
Hemoglobin Level (g/dL) (N = 57)	11.7 [10.8 – 12.4]	11.9 [10.7 – 12.7]*	11.2 [10.2 – 11.9]	<0.001
Platelet Count (x10^3 cells/μL) (N = 57)	324.0 [264.5 – 399.5]*	290.0 [205.0 – 349.5]	354.0 [257.0 – 433.0]	<0.001
WBC Count (x10^3 cells/μL) (N = 57)	7.4 [5.7 – 9.9]	3.6 [2.0 – 5.6]*	6.9 [5.2 – 10.1]*	<0.001
Differential Count				
Neutrophil (%) (N = 55)	65.5 [59.3 – 73.3]	64.6 [29.4 – 76.8]*	67.9 [59.5 – 75.2]	0.33
Lymphocyte (%) (N = 55)	23.7 [18.3 – 30.2]*	29.9 [20.5 – 55.1]*	21.6 [15.5 – 28.2]	<0.001
Monocyte (%) (N = 54)	7.2 [5.3 – 8.4]*	1.8 [0.8 – 6.4]*	8.5 [7.1 – 10.9]*	<0.001
Absolute Neutrophil Count (x10^3 cells/μL) (N = 55)	4.7 [3.5 – 6.9]	2.6 [0.7 – 4.4]*	4.9 [3.2 – 7.0]*	<0.001
Neutrophil-Lymphocyte Ratio (NLR) (N = 54)	2.7 [2.0 – 3.9]*	2.1 [0.5 – 3.8]*	3.1 [2.1 – 5.0]*	0.003
Platelet-Lymphocyte Ratio (PLR) (N = 55)	177.6 [135.7 – 282.0]*	274.2 [200.1 – 343.4]*	236.0 [163.0 – 286.2]*	<0.001
Monocyte-Lymphocyte Ratio (MLR) (N = 54)	0.3 [0.2 – 0.4]*	0.1 [0.0 – 0.2]*	0.4 [0.3 – 0.6]*	<0.001
Pan-immune-inflammation value (PIV) (N = 54)	418.0 [209.3 – 711.5]*	31.5 [9.9 – 87.2]*	534.2 [354.6 – 1467.7]*	<0.001
Anemia$ (n; %)	55/106 (51.9%)	34/61 (55.7%)	71/96 (74.0%)	-
Neutropenia$ (n; %)	2/105 (1.9%)	25/60 (41.7%)	1/94 (1.1%)	-
Mild neutropenia	2/2 (100%)	3/25 (12.0%)	0/1 (0%)	
Moderate neutropenia	0/2 (0%)	7/25 (28.0%)	1/1 (100%)	
Severe neutropenia	0/2 (0%)	15/25 (60.0%)	0/1 (0%)	
Thrombocytopenia$ (n; %)	2/106 (1.9%)	4/61 (6.6%)	5/96 (5.2%)	-

*, The data were not normally distributed according to the Shapiro–Wilk test (N < 100); therefore, the values are presented as median [IQR]; #, Comparison of the three paired groups was performed using Friedman's two-way analysis of variance by ranks; $, Anemia was defined as hemoglobin < 12.0 g/dL (according to WHO guidelines for non-pregnant women); neutropenia was defined as an absolute neutrophil count (ANC) < 1500 cells/μL (mild: 1000–1500 cells/μL; moderate: 500–999 cells/μL; severe: < 500 cells/μL); and thrombocytopenia was defined as a platelet count < 150 × 10^3 cells/μL.

Table 5. Comparative Analysis of Baseline Pre-Pharmacotherapy Hematological Profiles Between Survived and Non-Survived Patients

Parameter	Survived Median [IQR]	Non-survived Median [IQR]	p-value#
Hemoglobin Level (g/dL)	11.9 [10.9 – 12.7] (N = 99)	11.7 [11.1 – 12.5] (N = 7)	0.944
Platelet Count (x10³ cells/μL)	307.0 [236.0 – 373.0] (N = 99)	330.0 [264.0 – 340.0] (N = 7)	0.794
WBC Count (x10³ cells/μL)	7.4 [5.6 – 9.1] (N = 99)	7.8 [6.2 – 8.3] (N = 7)	0.944
Differential Count			
Neutrophil (%)	65.0 [58.8 – 71.7] (N = 98)	69.0 [63.7 – 77.8] (N = 7)	0.25
Lymphocyte (%)	24.9 [19.1 – 30.9] (N = 96)	19.3 [14.2 – 31.7] (N = 6)	0.286
Monocyte (%)	7.1 [5.6 – 8.8] (N = 96)	8.5 [6.8 – 15.1] (N = 6)	0.077
Absolute Neutrophil Count (x10³ cells/μL)	4.6 [3.3 – 6.3] (N = 98)	5.3 [4.3 – 7.5] (N = 7)	0.456
Neutrophil-Lymphocyte Count (NLR)	2.6 [1.9 – 3.8] (N = 96)	3.5 [2.0 – 5.5] (N = 6)	0.355
Platelet-Lymphocyte Count (PLR)	162.0 [127.1 – 244.4] (N = 96)	224.7 [160.3 – 291.7] (N = 6)	0.216
Monocyte-Lymphocyte Count (MLR)	0.3 [0.2 – 0.4] (N = 96)	0.4 [0.3 – 0.9] (N = 6)	0.043
Pan-immune-inflammation value (PIV)	378.8 [202.0 – 627.6] (N = 96)	850.6 [301.0 – 1296.6] (N = 6)	0.163

Comparison between the two independent (unpaired) groups was conducted using the Mann–Whitney U test for independent samples

Comparative analysis of baseline hematological profiles between survivors and non-survivors

A comparative analysis was performed to evaluate baseline hematologic differences between patients who survived and those who did not survive the round of pharmacotherapy during the study period (Table 5). Baseline hemoglobin levels were similar between groups, with survivors demonstrating a median of 11.9 g/dL [10.9–12.7] (N = 99) and non-survivors a median of 11.7 g/dL [11.1–12.5] (N = 7). This difference was not statistically significant (p = 0.944). Platelet counts at baseline also showed no meaningful difference between survivors and non-survivors. The median platelet count among survivors was 307.0 × 10³/μL [236.0–373.0], compared with 330.0 × 10³/μL [264.0–340.0] in non-survivors (p = 0.794). Similarly, median total leukocyte counts were comparable between groups, with survivors having 7.4 × 10³/μL [5.6–9.1] and non-survivors having 7.8 × 10³/μL [6.2–8.3] (p = 0.944). Analysis of differential leukocyte percentages revealed no statistically significant differences in baseline neutrophil or lymphocyte proportions. Survivors had a median neutrophil percentage of 65.0% [58.8–71.7] compared with 69.0% [63.7–77.8] in non-survivors (p = 0.250). Baseline lymphocyte percentages were 24.9% [19.1–30.9] in survivors and 19.3% [14.2–31.7] in non-survivors (p = 0.286). Monocyte percentages showed a trend toward higher values in non-survivors 7.1% [5.6–8.8] in survivors versus 8.5% [6.8–15.1] in non-survivors although this difference did not reach statistical significance (p = 0.077). The absolute neutrophil count was slightly higher in non-survivors (5.3 × 10³/μL [4.3–7.5]) compared with survivors (4.6 × 10³/μL [3.3–6.3]), but the difference was not significant (p = 0.456). Similarly, inflammatory composite indices, including NLR and PLR, did not differ significantly between groups. Survivors had a median NLR of 2.6 [1.9–3.8] compared with 3.5 [2.0–5.5] in non-survivors (p = 0.355). The median PLR was 162.0 [127.1–244.4] in survivors and 224.7 [160.3–291.7] in non-survivors (p = 0.216). In contrast, MLR demonstrated a statistically significant difference at baseline. Survivors had a median MLR of 0.3 [0.2–0.4], whereas non-survivors had a higher median of 0.4 [0.3–0.9] (p = 0.043). Although the median PIV at baseline was higher in non-survivors (850.6 [301.0–1296.6]) compared with survivors (378.8 [202.0–627.6]), this difference did not reach statistical significance (p = 0.163). It should be noted that survival subgroup comparisons were based on a limited number of events, with only seven non-survivors identified during the study period. Consequently, statistical power to detect differences between groups was restricted, and the absence of significant associations for several inflammatory indices should be interpreted with caution. These analyses were exploratory in nature and intended primarily to generate hypotheses for future investigation.

Discussion

Baseline demographic and clinical characteristics reveal a heterogeneous cohort with substantial comorbidity burden entering systemic therapy

The demographic structure of this cohort reflects well-established global trends in breast cancer epidemiology, in which the majority of cases arise in midlife and early older adulthood. The mean age of approximately 52 years aligns with data from both high-income regions and many low- and middle-income settings, where the typical age of presentation ranges between 45 and 60 years [10, 11]. This demographic pattern suggests that most patients in this cohort entered therapy during a physiologic life stage characterized by declining bone marrow reserve and increased comorbidity burden, both of which may influence hematologic response to pharmacologic treatment [12, 13]. Notably, younger-onset disease (≤40 years), which is often associated with more aggressive tumor biology, represented less than 10% of the cohort, consistent with its relatively lower global prevalence. Sociodemographic indicators further contextualize the clinical background of this population. Educational

attainment varied considerably, with nearly 37% having completed higher education while a substantial subset had only elementary schooling. Such heterogeneity mirrors patterns observed across diverse international breast cancer cohorts and has been associated in prior studies with differences in health literacy, treatment comprehension, and capacity for navigating complex cancer care pathways. The predominance of unemployed participants (66%) suggests potential socioeconomic vulnerabilities, which in many settings correlate with later presentation, more advanced disease, and potential barriers to supportive care. While this study did not directly evaluate socioeconomic effects on outcomes, these contextual factors remain important considerations in interpreting treatment patterns and tolerance. The marital status distribution, with 85.8% married, reflects common demographic trends in adult female cancer populations and may indicate the presence of household support structures, which have been associated in prior research with improved treatment adherence and psychosocial resilience [14, 15]. However, the impact of marital status on hematologic tolerance or pharmacotherapy outcomes is less clear, and this study did not include such correlations.

Comorbidity burden was substantial, with 59.4% of patients reporting at least one chronic medical condition. Hypertension, diabetes mellitus, and cardiovascular disease were the most prevalent comorbidities, a pattern consistent with the global rise of metabolic and cardiovascular disorders in aging female populations [16]. These conditions are clinically relevant because they may influence treatment decisions, baseline immune activation, and physiological resilience during systemic therapy. Pre-existing pulmonary disease, though less common, can complicate the management of treatment-related infectious or inflammatory events. The sizable "miscellaneous" category further underscores the clinical heterogeneity within the cohort. Collectively, this comorbidity burden reflects real-world populations in which multimorbidity is increasingly common and may have implications for both hematologic vulnerability and supportive care needs. A notable proportion of participants (69.8%) had undergone prior breast cancer treatment, most commonly surgery, followed by pharmacotherapy. The relatively high rate of previous systemic therapy exposure indicates that many patients were not treatment-naïve when entering the present evaluation. Prior treatments particularly chemotherapy or targeted therapies may exert lasting effects on bone marrow reserve and hematologic stability [17]. Although the current study evaluated hematologic patterns prospectively from the start of a new treatment course, pre-existing marrow stress or cumulative toxicity from earlier regimens may partly shape baseline findings and early treatment responses.

Breast cancer staging and tumor biology indicate a predominantly advanced, heterogeneous disease profile at treatment initiation

The breast cancer characteristics observed in this cohort align with global patterns demonstrating that a substantial proportion of women present with advanced disease at the time systemic therapy is initiated [18, 19]. More than half of the cohort presented with locally advanced breast cancer, while nearly one-third had metastatic disease. This distribution mirrors trends reported in many healthcare systems, particularly those where screening coverage is limited or where socioeconomic and logistical barriers delay diagnostic evaluation. Late-stage presentation carries important clinical implications, as more advanced disease is often associated with higher tumor burden, greater systemic inflammatory activation, and the need for more intensive pharmacotherapy regimensfactors that may contribute to treatment complexity and influence overall prognosis [20, 21]. Within the metastatic subgroup, the predominance of lung/pleural and bone metastases is consistent with the well-established metastatic tropism of breast cancer. Pulmonary and osseous dissemination represent two of the most common metastatic patterns worldwide, reflecting the biological affinity of breast cancer cells for these microenvironments [22, 23]. Liver involvement, present in a smaller proportion of patients, similarly aligns with known metastatic behavior, while brain metastasis was uncommon, as expected, given its lower prevalence at initial metastatic diagnosis. Although the study did not seek to correlate metastatic sites with hematologic or inflammatory status, these patterns underscore the considerable clinical heterogeneity within the cohort.

Histopathologic evaluation demonstrated that IDC constituted the overwhelming majority of tumors, which is consistent with its status as the most prevalent type of breast cancer globally. ILC and mixed histologies were less common, paralleling well-established epidemiologic distributions. The presence of a small number of mucinous tumors and other rare subtypes reflects the expected morphological diversity but does not substantially alter the overall histopathologic landscape. The predominance of IDC provides a relatively homogeneous foundation for understanding treatment-related responses, as IDC remains the reference subtype in most pharmacotherapy trials [24]. Tumor grade distribution further highlights the aggressiveness of disease within this cohort. Over 40% of patients had Grade III tumors, and an additional 35.8% had Grade II disease. The high proportion of intermediate- and high-grade tumors is consistent with cohorts presenting with advanced-stage disease and underscores the frequency of biologically aggressive malignancies. High-grade tumors often exhibit greater proliferative activity and treatment sensitivity, but they may also contribute to heightened systemic inflammation and immune perturbation at baseline a factor that could influence pharmacotherapy tolerance [25]. Immunohistochemical profiling revealed notable heterogeneity across molecular subtypes, with a predominance of luminal B tumors both HER2-positive and HER2-negative. Luminal B subtypes are recognized for their higher proliferative indices and comparatively poorer prognosis relative to luminal A tumors [26]. Their overrepresentation in this cohort reflects patterns observed in many regions where screening is limited and tumors are often detected at more advanced biological stages. The presence of HER2-enriched tumors (15.1%) and HER2-low expression (6.6%) further underscores the molecular diversity. Meanwhile, triple-negative breast

cancer (TNBC), present in 7.6% of patients, represents a clinically challenging subgroup requiring distinct therapeutic strategies. The sizable proportion of cases without complete immunohistochemical data (16%) highlights real-world constraints that frequently arise in routine oncology practice and may influence treatment allocation, particularly in settings where molecular testing capacity varies.

The distribution of treatment intentneoadjuvant, adjuvant, and palliativereflects the full clinical spectrum of breast cancer management [27]. Over one-third of patients received neoadjuvant therapy, consistent with the high prevalence of locally advanced disease, where tumor downstaging and early assessment of systemic responsiveness are central goals. Adjuvant therapy, used in 37.7% of the cohort, reflects curative-intent management following locoregional control. Palliative therapy accounted for nearly one-third of cases, aligning with the substantial proportion of individuals presenting with disseminated disease. These treatment intents establish a clinically heterogeneous baseline from which early hematologic trajectories would subsequently emerge. Pharmacotherapy regimens demonstrated substantial diversity, indicative of individualized treatment planning based on tumor biology, prior treatment exposure, and clinical stage. Taxane–carboplatin combinations and anthracycline–cyclophosphamide regimens were the most commonly employed protocols, reflecting their longstanding roles as backbone therapies across neoadjuvant, adjuvant, and palliative settings [28, 29]. The presence of numerous variant regimensincluding multi-agent anthracycline–taxane combinations, HER2-targeted therapy, hormonal agents, and less commonly used cytotoxic combinationsunderscores the breadth of pharmacologic strategies represented within the cohort. This regimen heterogeneity mirrors contemporary clinical practice, where treatment decisions are tailored to histopathologic, molecular, and patient-specific factors. The breadth of systemic therapy selections also highlights the inherent clinical complexity against which early hematologic changes must be interpreted.

Pretreatment hematologic and inflammatory profiles indicate mild anemia and variable inflammatory burden across patients

The baseline hematologic profile of this cohort offers important insight into the physiological status of patients entering systemic pharmacotherapy and highlights patterns commonly observed in real-world breast cancer populations. The mean hemoglobin level of 11.9 g/dL reflects a mild downward shift from population norms, consistent with the high prevalence of anemia observed in many breast cancer cohorts prior to treatment [30]. Such reductions may result from chronic disease–related inflammation, nutritional deficiencies, comorbid conditions, or tumor-related marrow involvement. Anemia at baseline has been documented in numerous studies and is often associated with poorer functional status and reduced physiologic reserve before treatment initiation [31]. The presence of reduced hemoglobin prior to therapy is clinically relevant, as lower baseline levels may predispose patients to more pronounced hematologic suppression once cytotoxic treatment begins. Platelet counts at baseline demonstrated wide variability but were generally preserved, with a median of 307 × 10^3/μL. This pattern is consistent with the expected thrombopoietic response in solid tumors, where platelet counts may remain normal or even elevated due to systemic inflammation, paraneoplastic thrombopoiesis, or cytokine-mediated stimulation of megakaryocytic activity [32, 33]. Elevated platelet counts have been associated in some studies with tumor aggressiveness and metastatic potential, particularly in breast cancer, though this relationship was not evaluated in the current dataset [34]. Nonetheless, the observed platelet distribution indicates adequate hemostatic reserve entering therapy, which is clinically relevant for planning systemic protocols that may induce thrombocytopenia. The baseline leukocyte profile, including a mean WBC count of 7.5 × 10^3/μL and a median ANC of 4.6 × 10^3/μL, suggests that most patients began treatment with adequate leukopoietic function. These values are consistent with global datasets showing preserved neutrophil and leukocyte counts among breast cancer patients prior to therapy unless significant bone marrow involvement or pre-treatment myelosuppressive therapies are present. The differential leukocyte percentages further support this finding, with median neutrophils around 65%, lymphocytes approximately 25%, and monocytes near 7%. These proportions resemble typical distributions seen in solid tumor patients and reflect a systemic inflammatory state that may accompany malignancy, in which neutrophil predominance and relative lymphopenia are frequently observed.

Importantly, the composite inflammatory indicesNLR, PLR, MLR, and PIVprovide additional context for understanding the immune-inflammatory landscape prior to treatment. The median NLR of 2.7 falls within the range commonly reported for untreated breast cancer patients [35, 36]. Elevated NLR has been repeatedly linked to poorer outcomes in breast cancer, though its prognostic significance varies by stage and molecular subtype [37, 38]. Similarly, the baseline PLR median of 163.2 aligns with values reported in cohorts with localized or locally advanced disease. The MLR median of 0.3 indicates a balance between monocyte-driven inflammatory activation and lymphocyte-mediated immune regulation, consistent with findings from other pretreatment breast cancer studies. PIV, a more recently proposed composite metric incorporating neutrophils, platelets, monocytes, and lymphocytes, showed substantial variability within the cohort. The median PIV of 386.8, with a broad interquartile range, highlights significant interpatient differences in systemic inflammatory burden. Such variability may reflect differences in tumor biology, disease extent, comorbidity profiles, or chronic inflammation unrelated to cancer. Baseline PIV values have been associated in prior research with disease progression risk and survival outcomes across several malignancies, including breast cancer, although its incorporation into clinical practice remains investigational [39, 40].

Dynamic nadir-and-recovery hematologic patterns emerge during the first cycle of systemic therapy

The hematologic fluctuations observed following pharmacotherapy reflect well-recognized patterns of early marrow suppression and subsequent recovery that accompany many systemic breast cancer treatments. The significant temporal decline in hemoglobin by week 3 is consistent with cumulative erythroid suppression, hemodilution, and early treatment-associated inflammation. Although the slight numerical increase at week 1 may reflect transient hemodynamic shifts or ongoing erythropoiesis, the overall decrease by week 3 aligns with established evidence that anemia commonly emerges or worsens during the early phase of cytotoxic therapy. This pattern is clinically relevant, as early anemia can contribute to fatigue, reduced functional status, and may influence decisions regarding treatment intensity in subsequent cycles. Platelet dynamics demonstrated a biphasic pattern, with an initial decline at week 1 followed by a rebound above baseline levels at week 3. The early nadir is consistent with direct megakaryocytic suppression by cytotoxic agents and increased peripheral consumption. The subsequent rise may represent reactive thrombocytosis, a phenomenon frequently observed after marrow suppression resolves, driven by elevated thrombopoietic cytokines such as interleukin-6. Similar post-nadir platelet overshoots have been reported across multiple chemotherapy regimens and may be influenced by underlying inflammatory states associated with malignancy [41]. The profound decrease in total leukocyte count and ANC at week 1 represents the expected neutrophil nadir following many standard breast cancer regimens, particularly anthracycline- and taxane-based treatments. The nadir timing and magnitude observed here are consistent with prior reports showing neutrophil suppression peaking between 7 and 14 days after treatment initiation [42]. The robust recovery by week 3 reflects marrow regeneration and supports the accuracy of expected cycle timing in standard treatment intervals. The transient increase in lymphocyte percentage at week 1 likely represents a mathematical consequence of neutrophil depletion, rather than a true lymphocytic expansion, while the sharp reduction in monocyte percentages aligns with their sensitivity to cytotoxic injury and bone marrow suppression.

The composite inflammatory indices (NLR, PLR, MLR, and PIV) provide deeper insight into dynamic immune–inflammatory changes during treatment. The initial decrease in NLR at week 1 followed by an increase above baseline at week 3 suggests a dynamic interplay between neutrophil suppression and lymphocyte redistribution early in treatment. PLR exhibited a pronounced rise at week 1, consistent with early neutrophil decline and relative preservation of platelet counts; PLR trajectories such as these have been reported as markers of acute inflammatory response and marrow stress. MLR demonstrated the most dramatic oscillation, with an early decline followed by a marked rise at week 3, reflecting both monocyte sensitivity to treatment and potential compensatory hematopoietic activity during marrow recovery. PIV showed the most extreme fluctuations, decreasing sharply at week 1 and rising dramatically above baseline by week 3. Given that PIV incorporates neutrophils, platelets, monocytes, and lymphocytes, its significant reduction during early neutrophil suppression followed by an amplified rebound during marrow recovery underscores its sensitivity to systemic inflammatory and hematopoietic dynamics. Such fluctuations in PIV have been documented in other malignancies and may indicate treatment-induced shifts in systemic immune activation [43]. The prevalence of hematologic toxicities further elucidates the clinical significance of these laboratory changes. Neutropenia was rare at baseline but increased sharply at week 1, affecting over 40% of patients, with a considerable proportion experiencing moderate to severe episodes. This high early-cycle neutropenia rate is consistent with the known myelotoxicity of commonly used regimens such as anthracycline–cyclophosphamide and taxane-platinum combinations [44]. The near-complete resolution by week 3 highlights effective marrow recovery and supports the feasibility of standard 21-day treatment intervals. The rise in anemia prevalence to 74% by week 3 reflects cumulative erythroid suppression and reinforces the importance of monitoring and managing early-cycle anemia. Thrombocytopenia rates remained comparatively low, consistent with the more selective myelosuppressive effects of the regimens used.

Higher baseline MLR emerges as a potential early indicator of poorer survival

The comparative analysis of baseline hematologic indices between survivors and non-survivors provides important insight into the potential prognostic relevance of inflammatory and immune-related markers prior to initiating systemic pharmacotherapy. Overall, most standard hematologic parametersincluding hemoglobin, platelet count, total leukocyte count, and absolute neutrophil countdid not differ significantly between the two groups, suggesting that generalized marrow function and baseline cytopoietic capacity were broadly similar regardless of eventual survival status. This pattern aligns with existing evidence indicating that conventional hematologic indices, while essential for treatment planning, may have limited sensitivity in predicting short-term survival or mortality risk in breast cancer patients before therapy begins. Differential leukocyte percentages also demonstrated relative similarity across groups, with no significant differences in baseline neutrophil or lymphocyte proportions. These findings are consistent with prior research showing that individual leukocyte subsets, when examined in isolation, may not sufficiently capture the complexity of tumor–immune interactions or systemic inflammation that contribute to prognosis. Although monocyte percentages showed a trend toward higher levels in non-survivors, the difference did not reach statistical significance. Still, this pattern may reflect biologically relevant signals, as elevated monocyte counts have been associated in other studies with pro-inflammatory tumor microenvironments and tumor-associated macrophage (TAM) recruitmentfactors linked to tumor aggressiveness and poorer outcomes [45, 46].

Among the composite inflammatory markers evaluated,

MLR emerged as the only parameter demonstrating a statistically significant difference between survivors and non-survivors at baseline. Non-survivors exhibited higher MLR values, indicating a relative increase in monocyte-mediated inflammatory activity alongside reduced lymphocyte-mediated immunosurveillance. This observation is consistent with mounting evidence across oncologic literature that elevated MLR may serve as a surrogate for heightened systemic inflammation, immune dysregulation, and pro-tumorigenic immune cell polarization [47]. Monocytes, particularly those differentiating into TAMs, play central roles in tumor growth, angiogenesis, and metastatic progression [48]. Conversely, lower lymphocyte levels reflect diminished adaptive immune capacity, which has been repeatedly associated with poorer prognosis across multiple breast cancer subtypes. Thus, the elevated MLR seen in non-survivors may represent a composite signal of both increased inflammatory drive and impaired host immune defense at the outset of treatment. From a clinical perspective, if validated in larger prospective studies, baseline MLR could potentially serve as a simple and cost-effective triage tool during the initiation of systemic pharmacotherapy. Patients with elevated pretreatment MLR may represent a subgroup with heightened systemic inflammation and impaired immunologic reserve, potentially predisposing them to poorer tolerance of treatment or adverse outcomes. In such cases, clinicians might consider closer early-cycle monitoring, more proactive laboratory surveillance, or earlier implementation of supportive measures. Although the present study was not designed to determine optimal cut-off values or to guide intervention thresholds, integrating MLR into a composite risk stratification frameworkalongside clinical stage, comorbidities, and regimen intensitycould support individualized supportive care planning. Importantly, these implications remain exploratory and should not yet be interpreted as prescriptive; prospective validation studies are required to determine whether MLR-guided strategies can improve treatment safety, continuity, or survival outcomes.

At last, although PIV did not differ significantly between groups, the markedly higher median PIV observed among non-survivors suggests potentially meaningful biological variability. PIV integrates neutrophil, monocyte, and platelet countsreflecting pro-inflammatory and pro-thrombotic activitywith lymphocyte counts, representing immune competence. Prior studies have identified elevated PIV as a marker of worse outcomes in breast and other solid tumors, though its prognostic performance may vary across disease stages and treatment settings [40, 49]. The lack of statistical significance in this cohort may reflect the limited number of non-survivors, variability in underlying disease biology, or insufficient power to detect differences.

Study Limitations and Future Directions

Study limitations

Several important limitations should be acknowledged when interpreting the findings of this study. First, although the study employed a prospective cohort design, the sample sizewhile adequate for detecting major hematologic changeswas relatively modest for evaluating prognostic associations, particularly in subgroup analyses such as comparisons between survivors and non-survivors. Although 106 patients were enrolled at baseline, only 57 had complete paired hematologic data across all three time points for full longitudinal evaluation. Furthermore, the non-survivor group comprised only seven patients. This limited number of events substantially reduces statistical power for survival-related comparisons and increases the possibility of type II error, potentially obscuring meaningful differences in inflammatory indices beyond the observed MLR association. Accordingly, the survival analysis presented in this study should be considered exploratory and hypothesis-generating rather than confirmatory. The findings require validation in larger, multi-center cohorts with greater event numbers and extended follow-up to determine the true prognostic significance of baseline inflammatory markers. Additionally, the study captured hematologic changes only during the first three weeks of treatment, which represents the early pharmacotherapy window but does not encompass later cycles where cumulative myelosuppression may be more pronounced. Evaluating hematologic trajectories across multiple cycles would provide a more comprehensive understanding of the evolution of treatment-related cytopenias, inflammatory fluctuations, and the potential for delayed marrow toxicity.

An additional limitation relates to the absence of standardized documentation of supportive care interventions. The study did not systematically record the use of prophylactic or therapeutic G-CSF, blood transfusions, or antibiotic therapy during neutropenic episodesinterventions that may substantially influence the depth of hematologic nadirs as well as the timing and magnitude of recovery. In addition, febrile neutropenia could not be assessed because body temperature was not consistently monitored during periods of neutropenia. Beyond supportive interventions, other clinically relevant toxicity endpointssuch as hospitalization, chemotherapy dose delays or reductions, and transfusion requirementswere also not prospectively captured in a structured manner. As a result, the hematologic trajectories reported in this study reflect laboratory-defined cytopenias within real-world practice settings but cannot be directly linked to clinically actionable outcomes. Although the observed neutropenia and anemia rates provide valuable insight into early marrow suppression dynamics, their precise impact on treatment delivery, morbidity, and supportive care utilization remains uncertain. Future prospective studies incorporating structured documentation of supportive measures, standardized toxicity reporting, and treatment-modification data are needed to more comprehensively evaluate treatment-related hematologic toxicity and to clarify the clinical consequences of early-cycle hematologic fluctuations, thereby informing risk-adapted supportive care strategies.

Next, the analysis did not fully account for the heterogeneity of treatment regimens. Patients received a wide range of systemic regimensincluding taxane–carboplatin combinations, anthracycline–cyclophosphamide protocols, HER2-targeted therapies, and

endocrine treatmentseach with distinct myelosuppressive profiles. While this diversity reflects real-world oncology practice and enhances external validity, it may confound the observed hematologic trajectories. We considered performing stratified or sensitivity analyses for the most frequently administered regimens; however, the number of patients within individual regimen subgroupsparticularly those with complete longitudinal datawas insufficient to allow statistically robust comparisons. Further subgroup stratification would have resulted in very small sample sizes and unstable estimates. Consequently, the present findings should be interpreted as reflecting aggregate pharmacotherapy-associated hematologic dynamics rather than regimen-specific effects. Larger studies with adequately powered regimen-specific cohorts are warranted to disentangle differential myelosuppressive patterns across treatment protocols.

The study also relied on routine hematologic parameters and derived inflammatory indices as surrogate markers of systemic immune and inflammatory status. While these markers are practical, low-cost, and clinically meaningful, they cannot fully capture the complexity of immune dynamics, cytokine signaling, marrow microenvironmental changes, or tumor–immune interactions. Integrating more advanced biomarkerssuch as cytokine panels, lymphocyte subset profiling, circulating tumor DNA, or marrow microenvironment assessmentscould significantly enhance mechanistic understanding of the observed hematologic fluctuations [50, 51]. Fifth, the study did not directly link hematologic trajectories to clinical outcomes such as treatment delays, dose modifications, hospitalization for febrile neutropenia, or progression-free survival. Although the primary objective was to characterize hematologic changes, understanding how these fluctuations translate into clinically actionable endpoints would strengthen the translational relevance of the findings. Such linkage is particularly relevant for the development of risk-adapted supportive care or tailored dose-intensity strategies.

Future directions

Looking forward, several opportunities for expanding this work can be identified. Larger, multi-institutional prospective studies should be conducted to validate the early hematologic patterns identified in this cohort and to assess whether these trends hold across diverse populations, treatment settings, and pharmacotherapy regimens. In particular, exploring the prognostic value of baseline and early-cycle inflammatory indicessuch as MLR and PIVcould lead to the development of hematologic-based risk stratification tools to support individualized treatment planning. Future research should extend hematologic monitoring beyond the first treatment cycle to evaluate cumulative marrow toxicity, delayed nadirs, and adaptation or sensitization effects that may emerge with repeated cycles. Such longitudinal analyses may reveal patterns predictive of long-term tolerability, need for supportive interventions, or heightened susceptibility to severe myelosuppression. Another important direction involves integrating hematologic data with molecular and immunologic profiling to better characterize the biological mechanisms underlying early treatment-induced hematologic shifts. Multi-omic analyses and immune phenotyping could elucidate how tumor biology, host immune status, and treatment modality interact to shape hematologic and inflammatory responses [52, 53]. Finally, clinical implementation studies are warranted to determine whether early-cycle hematologic markers can be incorporated into decision-support algorithms for prophylactic G-CSF, transfusion thresholds, or individualized dosing strategies. The ultimate goal of such research is to enhance patient safety, minimize treatment interruptions, and optimize therapeutic efficacy through personalized supportive care.

In conclusion, in this prospective cohort study, early pharmacotherapy for breast cancer produced distinct and dynamic hematologic alterations, characterized by marked week-1 myelosuppression followed by partial recovery by week 3, alongside significant fluctuations in inflammatory indices. Baseline hematologic parameters were largely preserved, but systemic inflammation was evident, and elevated pre-treatment MLR emerged as a potential early prognostic indicator. Together, these findings underscore the importance of close hematologic monitoring during the initial treatment cycle and highlight the potential utility of readily available inflammatory markers for early risk stratification. Further research is warranted to validate these observations, explore underlying biological mechanisms, and determine how early hematologic trajectories can inform more personalized supportive care and treatment planning.

Author Contribution Statement

HS: Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing. MS: Conceptualization, Writing - Original Draft, Writing - Review & Editing. AA: Writing - Original Draft, Writing - Review & Editing, Supervision. EH: Writing - Original Draft, Writing - Review & Editing. PZR: Resources, Writing - Original Draft, Writing - Review & Editing. MND: Resources, Writing - Original Draft, Writing - Review & Editing. PNAA: Writing - Original Draft, Writing - Review & Editing. SUYB: Writing - Original Draft, Writing - Review & Editing.

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Scientific Body Approval

It is part of an approved student thesis.

Ethical Statement

Ethical approvals were obtained from the institutional review boards of both participating hospitals (197/KEP/2024 from Universitas Airlangga Hospital and 445/02/KOM.ETIK/2025 from Haji General Hospital), and all participants provided written informed consent.

Availability of Data

The data that support the findings of this study are available on request from the corresponding author HS.

Conflict of Interest

The authors have no conflicts of interest to declare.

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