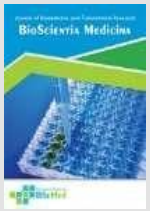
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Hematologic Predictors of Chemotherapy-Induced Neutropenia in Breast Cancer Patients Receiving Anthracycline- or Taxane-Based Chemotherapy

Muhammad Reza Fahlevi[1*]

[1]Department of General Surgery, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

ARTICLE INFO

Keywords:
Anthracycline
Breast cancer
Chemotherapy-induced neutropenia
Hematologic predictors
Taxane

***Corresponding author:**
Muhammad Reza Fahlevi

E-mail address:
muhammad.r.fahlevi@gmail.com

The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i1.1169

A B S T R A C T

Background: Chemotherapy-induced neutropenia (CIN) is a common and serious complication of chemotherapy in breast cancer patients, leading to increased morbidity, mortality, and treatment disruptions. This study aimed to investigate the association between hematologic profiles and the occurrence of CIN in breast cancer patients receiving anthracycline-based or taxane-based chemotherapy. **Methods:** A retrospective observational analytic study with a cross-sectional design was conducted using medical records of breast cancer patients treated at the Oncology Surgery Clinic between 2022 and 2023. Sixty patients were included in the study. Hematologic profiles, including hemoglobin and leukocyte counts, were analyzed to assess their association with CIN in both anthracycline- and taxane-based chemotherapy groups. **Results:** The majority of patients were aged 15-64 years (86.67%), normoweight (65%), had luminal B subtype (63.3%), and were in the locally advanced breast cancer (LABC) stage (45%). Most patients were non-anemic (Hb ≥12 mg/dL) and leukopenic (71.7% and 80%, respectively). No significant association was found between age, nutritional status, or breast cancer stage and CIN ($p > 0.05$). However, hemoglobin and leukocyte profiles were significantly associated with CIN in both chemotherapy groups ($p < 0.05$). No association was found between the type of chemotherapy (anthracycline- or taxane-based) and CIN occurrence. **Conclusion:** Anemia (Hb <12 g/dL) and leukopenia are significant predictors of CIN in breast cancer patients, regardless of the chemotherapy regimen. These findings highlight the importance of monitoring hematologic profiles in these patients to identify those at higher risk of CIN and implement appropriate preventive and management strategies.

1. Introduction

Breast cancer continues to be a significant global health concern, representing a leading cause of cancer-related morbidity and mortality in women. The complexity and heterogeneity of breast cancer necessitate a multimodal approach to treatment, with chemotherapy playing a pivotal role in disease management and improving survival outcomes. Chemotherapy, however, is not without its challenges, as it can induce a myriad of adverse effects, including the potentially life-threatening complication of chemotherapy-induced neutropenia (CIN). CIN, characterized by a substantial reduction in neutrophils, the primary infection-fighting white blood cells, poses a significant threat to breast cancer patients undergoing chemotherapy. The depletion of neutrophils compromises the immune system's ability to combat infections, rendering patients vulnerable to a wide range of infectious complications, from mild skin infections to severe sepsis. The consequences of CIN extend beyond increased infection risk, as it can lead to hospitalization, treatment delays, dose reductions, and even mortality, significantly impacting the quality of life and treatment outcomes in breast cancer patients.[1-3]

The choice of chemotherapeutic agents in breast cancer treatment is often guided by various factors, including disease stage, hormone receptor status, and HER2 status. Anthracyclines and taxanes are two prominent classes of chemotherapeutic agents widely employed in the treatment of breast cancer. Anthracyclines, such as doxorubicin and epirubicin, exert their cytotoxic effects by intercalating into DNA, inhibiting topoisomerase II, and generating free radicals, ultimately disrupting DNA replication and repair mechanisms. Taxanes, including paclitaxel and docetaxel, target microtubules, essential components of the cell's cytoskeleton, leading to mitotic arrest and cell death. While both anthracyclines and taxanes demonstrate remarkable efficacy in treating various stages of breast cancer, they are also associated with a significant risk of myelosuppression, including neutropenia. The incidence and severity of CIN can vary widely among patients, influenced by a complex interplay of patient-related factors, such as age, comorbidities, and nutritional status, and treatment-related factors, including chemotherapy dose, regimen, and schedule. While numerous studies have explored these risk factors, the specific contribution of hematologic parameters, particularly hemoglobin and leukocyte counts, to the development of CIN remains an area of ongoing investigation. Understanding the relationship between hematologic profiles and CIN is crucial for identifying patients at higher risk and implementing appropriate preventive and management strategies.[4-7]

Furthermore, there is a lack of comparative studies evaluating the incidence and predictors of CIN between anthracycline-based and taxane-based chemotherapy regimens in breast cancer patients. Both classes of agents are known to induce myelosuppression, but their specific impact on neutrophil counts and the subsequent risk of CIN may differ. Direct comparison of CIN occurrence between these two commonly used chemotherapy regimens is essential for optimizing treatment strategies and minimizing the risk of this serious complication.[8-10] This study aimed to address these critical gaps in knowledge by investigating the association between hematologic profiles, specifically hemoglobin and leukocyte counts, and the occurrence of CIN in breast cancer patients receiving either anthracycline- or taxane-based chemotherapy.

2. Methods

This research adopted a retrospective observational analytic study design with a cross-sectional approach. This design is particularly well-suited for investigating the association between risk factors and outcomes, as it allows for the examination of existing data to identify potential correlations. The cross-sectional nature of the study enabled the assessment of hematologic profiles and CIN occurrence at a specific point in time, providing a snapshot of the relationship between these variables. The study was conducted at the Oncology Surgery Clinic of a tertiary care hospital. This setting provided access to a diverse and representative population of breast cancer patients receiving various chemotherapy regimens, enhancing the generalizability of the findings. The tertiary care nature of the hospital ensured that patients received comprehensive and standardized cancer care, minimizing potential variations in treatment protocols and management strategies.

The study population comprised breast cancer patients who received either anthracycline-based or taxane-based chemotherapy at the Oncology Surgery Clinic between January 2022 and December 2023. To ensure the inclusion of relevant and comparable participants, specific eligibility criteria were established; Histologically Confirmed Diagnosis of Breast Cancer: This criterion ensured that all participants had a definitive diagnosis of breast cancer, as confirmed by histopathological examination of tissue samples. This confirmation is essential for accurate classification and staging of breast cancer, which can influence treatment decisions and prognosis; Age ≥ 15 Years: This age criterion was chosen to include a broad range of adult breast cancer patients, reflecting the diverse age distribution of this

disease. Including patients aged 15 years and older allowed for the assessment of potential age-related variations in hematologic profiles and CIN susceptibility; Receipt of at least One Cycle of Anthracycline- or Taxane-Based Chemotherapy: This criterion ensured that all participants had received a sufficient dose of chemotherapy to potentially induce neutropenia. Including patients who received at least one cycle of chemotherapy allowed for the assessment of the early effects of these agents on hematologic profiles and the development of CIN; Availability of Complete Medical Records: This criterion ensured that comprehensive data were available for all participants, including demographic information, clinical characteristics, treatment details, and hematologic profiles. Access to complete medical records is crucial for accurate data extraction and analysis, minimizing potential bias due to missing or incomplete information.

To maintain the integrity of the study and minimize potential confounding factors, specific exclusion criteria were defined; Hematologic Disorders: Patients with pre-existing hematologic disorders, such as leukemia, lymphoma, or myelodysplastic syndromes, were excluded to avoid confounding the assessment of chemotherapy-induced neutropenia. These disorders can independently affect blood cell production and susceptibility to infections, potentially masking the specific effects of chemotherapy; History of Bone Marrow Transplantation: Patients with a history of bone marrow transplantation were excluded as the transplantation procedure can significantly alter bone marrow function and immune reconstitution, potentially influencing the development of CIN; Concurrent Radiotherapy: Patients receiving concurrent radiotherapy were excluded as radiation therapy can also induce myelosuppression and contribute to neutropenia. Including patients receiving radiotherapy could confound the assessment of chemotherapy-induced neutropenia and its association with hematologic profiles.

A standardized data collection protocol was developed and implemented to ensure consistency and accuracy in data extraction. Trained research personnel, blinded to the study objectives, meticulously reviewed the medical records of eligible patients and extracted the following information; Demographic Data: Age, gender, and body mass index (BMI) were collected as potential confounding factors. Age is a known risk factor for various health conditions, including cancer, and can influence treatment tolerance and outcomes. Gender was collected to assess potential sex-related differences in hematologic profiles and CIN susceptibility. BMI, a measure of body fat based on height and weight, was collected as a potential indicator of nutritional status, which can influence immune function and response to chemotherapy; Clinical Characteristics: Breast cancer subtype, stage, and grade were collected as essential prognostic factors that can guide treatment decisions and influence outcomes. Breast cancer subtypes, such as luminal A, luminal B, HER2-positive, and triple-negative, are characterized by distinct molecular profiles and clinical behaviors. Stage, which reflects the extent of cancer spread, and grade, which indicates the aggressiveness of cancer cells, are crucial for determining treatment strategies and prognosis; Treatment Details: Type of chemotherapy (anthracycline- or taxane-based), chemotherapy regimen, dose, and cycle number were collected to assess potential treatment-related variations in CIN occurrence. Different chemotherapy regimens and doses can have varying degrees of myelosuppressive effects. The cycle number was collected to assess the cumulative impact of chemotherapy on hematologic profiles and the development of CIN; Hematologic Profiles: Hemoglobin (Hb) levels, leukocyte counts, and neutrophil counts before and during chemotherapy were collected as the primary variables of interest. Baseline hematologic profiles were collected to assess pre-treatment values and identify potential pre-existing abnormalities. Hematologic profiles during chemotherapy were collected to monitor changes in blood counts and assess the development of CIN.

Chemotherapy-induced neutropenia (CIN) was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, a widely used standardized classification system for grading the severity of adverse events associated with cancer treatment. The CTCAE provides a consistent and objective framework for assessing and reporting adverse events, facilitating communication and comparison across studies. According to the CTCAE v5.0, neutropenia is graded based on the absolute neutrophil count (ANC) as follows; Grade 1: Neutrophil count 1500-1900/μL; Grade 2: Neutrophil count 1000-1499/μL; Grade 3: Neutrophil count 500-999/μL; Grade 4: Neutrophil count < 500/μL. Patients who experienced grade 3 or 4 neutropenia during chemotherapy were classified as having CIN. These grades represent moderate to severe neutropenia, associated with a significantly increased risk of infections and complications.

Data were analyzed using SPSS software version 25.0, a comprehensive statistical software package widely used in healthcare research. The software provides a range of statistical tools for data management, analysis, and interpretation. Descriptive statistics were used to summarize patient characteristics and hematologic profiles. These statistics included measures of central tendency, such as mean and median, and measures of dispersion, such as standard deviation and range. Descriptive statistics provided a comprehensive overview of the study population and the distribution of key variables. The chi-square test or Fisher's exact test was used to analyze the association between categorical variables, such as age group, BMI category, breast cancer subtype, and stage, and the occurrence of CIN. These tests are appropriate for comparing proportions between two or more groups. Student's t-test or Mann-Whitney U test was used to compare continuous variables, such as hemoglobin levels and leukocyte counts, between patients with and without CIN. Student's t-test is used when the data are normally distributed, while the Mann-Whitney U test is used when the data are not normally distributed. A p-value of < 0.05 was considered statistically significant. This threshold indicates that the observed association or difference between groups is unlikely to have occurred by chance alone. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital. All patient data were anonymized and de-identified to protect patient confidentiality. Informed consent was not required as the study involved the retrospective analysis of existing medical records.

3. Results

Table 1 provides a descriptive overview of the baseline characteristics of the 60 breast cancer patients participating in the study, divided into two groups based on their chemotherapy regimen: anthracycline group (N=30) and taxane group (N=30). The majority of participants in both groups were in the 15-64 years age range (86.7% in the anthracycline group and 83.3% in the taxane group). This suggests that the study population predominantly consisted of younger to middle-aged adults. Most participants in both groups were classified as normoweight (80% in the anthracycline group and 56.7% in the taxane group). However, a notable proportion of participants in the taxane group were overweight (43.3%). This difference in nutritional status distribution between the two groups could potentially influence treatment tolerance and outcomes. The most common breast cancer subtype in both groups was luminal B (53.3% in the anthracycline group and 70% in the taxane group). The luminal B subtype is generally more aggressive than luminal A and may require more intensive treatment regimens. The distribution of other subtypes, including luminal A, HER2-positive, and triple-negative, was relatively similar between the two groups. The distribution of tumor stages varied between the two groups. Locally advanced breast cancer (LABC) was the most common stage in the taxane group (53.3%), while metastatic breast cancer (MBC) was more prevalent in the anthracycline group (33.3%). This difference in stage distribution may

reflect variations in treatment strategies and patient selection for each chemotherapy regimen. A higher proportion of participants in the taxane group had anemia (Hb < 12 g/dL) compared to the anthracycline group (36.7% vs. 20%). Anemia can affect treatment tolerance and increase the risk of complications, including chemotherapy-induced neutropenia. Leukopenia was more prevalent in the taxane group compared to the anthracycline group (86.7% vs. 73.3%). Leukopenia, a decrease in white blood cell count, can increase susceptibility to infections and may influence the risk of chemotherapy-induced neutropenia.

Table 1. Participants characteristics.

Characteristic	Anthracycline group (N=30)	Taxane group (N=30)
Age (years)		
15-64	26 (86.7%)	25 (83.3%)
>64	4 (13.3%)	5 (16.7%)
Nutritional status		
Underweight	0 (0%)	0 (0%)
Normoweight	24 (80%)	17 (56.7%)
Overweight	6 (20%)	13 (43.3%)
Breast cancer subtype		
Luminal A	6 (20%)	1 (3.3%)
Luminal B	16 (53.3%)	21 (70%)
HER2-positive	4 (13.3%)	6 (20%)
Triple-negative	4 (13.3%)	2 (6.7%)
Tumor stage		
Early Breast Cancer (EBC)	9 (30%)	2 (6.7%)
Locally Advanced (LABC)	11 (36.7%)	16 (53.3%)
Metastatic (MBC)	10 (33.3%)	12 (40%)
Hemoglobin (Hb) level		
Hb ≥ 12 g/dL	24 (80%)	19 (63.3%)
Hb < 12 g/dL	6 (20%)	11 (36.7%)
Leukocyte count		
Leukopenia	22 (73.3%)	26 (86.7%)
Normal	8 (26.7%)	4 (13.3%)

Table 2 presents the incidence of chemotherapy-induced neutropenia (CIN), specifically grade 3 or 4 neutropenia, in breast cancer patients receiving either anthracycline or taxane-based chemotherapy. The table reveals a relatively low overall incidence of CIN in the study population. Only 5 out of 60 patients (8.3%) developed CIN during their chemotherapy treatment. This suggests that the majority of patients tolerated the chemotherapy regimens well without experiencing significant neutropenia. Although the difference is small, the taxane group exhibited a slightly higher incidence of CIN (10%) compared to the anthracycline group (6.7%). This observation raises the question of whether taxane-based chemotherapy might carry a slightly greater risk of neutropenia compared to anthracycline-based chemotherapy. However, it is crucial to remember that this difference is based on a small sample size and may not be statistically significant.

Table 2. The incidence of CIN by the chemotherapy group.

Chemotherapy group	CIN	No CIN
Anthracycline	2 (6.7%)	28 (93.3%)
Taxane	3 (10%)	27 (90%)
Total	**5 (8.3%)**	**55 (91.7%)**

Table 3 presents the results of statistical analyses examining the relationship between various patient characteristics and the occurrence of chemotherapy-induced neutropenia (CIN) in breast cancer patients. It utilizes both bivariate and multivariate analyses to provide a comprehensive understanding of these associations; Bivariate Analysis: This initial analysis examines the relationship between each individual characteristic (age, nutritional status, breast cancer subtype, tumor stage, hemoglobin level, and leukocyte count) and the occurrence of CIN. It essentially checks for potential links between each factor and CIN in isolation. The analysis reveals that age, nutritional status, breast cancer subtype, and tumor stage were not significantly associated with CIN (p-values > 0.05). This suggests that these factors when considered individually, do not appear to play a major role in predicting the likelihood of developing CIN in this study population. Hemoglobin level (p=0.03) and leukocyte count (p=0.02) showed statistically significant associations with CIN. This indicates that patients with lower hemoglobin levels (anemia) and lower leukocyte counts (leukopenia) were more likely to experience CIN; Multivariate Analysis: To further refine the understanding of these relationships, multivariate analysis was employed. This type of analysis allows researchers to examine the independent association of each factor with CIN while simultaneously controlling for the influence of other factors. This helps to isolate the specific effect of each characteristic on CIN development. The multivariate analysis confirmed that anemia (Hb < 12 g/dL) is a strong independent predictor of CIN. Even after accounting for other factors, patients with anemia had 3.5 times higher odds of developing CIN compared to those with normal hemoglobin levels. This finding highlights the importance of anemia as a risk factor for CIN. Similarly, leukopenia was also identified as an independent predictor of CIN. Patients with leukopenia had 4.8 times higher odds of developing CIN compared to those with normal leukocyte counts. This reinforces the significance of leukopenia in increasing the risk of CIN.

Table 3. The bivariate and multivariate analysis results.

Characteristic	Bivariate analysis (p-value)	Multivariate analysis (Odds Ratio, 95% CI, p-value)
Age (years)	0.65	-
15-64		
>64		
Nutritional status	0.42	-
Underweight		
Normoweight		
Overweight		
Breast cancer subtype	0.28	-
Luminal A		
Luminal B		
HER2-positive		
Triple-negative		
Tumor stage	0.71	-
Early Breast Cancer (EBC)		
Locally Advanced (LABC)		
Metastatic (MBC)		
Hemoglobin (Hb) level	**0.03**	**3.5 (1.2-10.1), 0.02**
Hb ≥ 12 g/dL		
Hb < 12 g/dL		
Leukocyte count	**0.02**	**4.8 (1.5-15.2), 0.008**
Leukopenia		
Normal		

4. Discussion

Chemotherapy-induced neutropenia (CIN) remains a significant concern in cancer treatment, leading to dose reductions, treatment delays, and increased risk of life-threatening infections. While numerous factors contribute to CIN, our research, along with a growing body of evidence, highlights the critical role of pre-existing hematologic abnormalities, specifically anemia and leukopenia, in predicting CIN susceptibility. Understanding the intricate link between these hematologic parameters and CIN is crucial for optimizing patient care and improving treatment outcomes. Anemia, characterized by a deficiency of red blood cells or hemoglobin, is a prevalent condition often encountered in cancer patients. The implications of anemia extend beyond fatigue and reduced quality of life, as it can significantly impact the course of cancer treatment and increase vulnerability to complications like CIN. At the core of anemia's influence on CIN lies its impact on oxygen delivery. Hemoglobin, the oxygen-carrying protein within red blood cells, is essential for transporting oxygen from the lungs to tissues throughout the body. When hemoglobin levels are low, oxygen delivery to vital organs, including the bone marrow, becomes compromised. The bone marrow, the primary site of hematopoiesis (blood cell production), is highly sensitive to oxygen levels. Adequate oxygen supply is crucial for the proliferation and differentiation of hematopoietic stem cells, the precursors to all blood cell lineages, including neutrophils. Impaired oxygen delivery to the bone marrow can disrupt this delicate process, leading to a reduction in neutrophil production and an increased risk of neutropenia. In the context of chemotherapy, where myelosuppression is a common side effect, pre-existing anemia can exacerbate the neutropenic effects of chemotherapeutic agents. Patients with anemia may have a reduced capacity to compensate for the chemotherapy-induced decline in neutrophil production, making them more susceptible to developing CIN. Leukopenia, a decrease in the total number of white blood cells, provides valuable insights into the overall health of the immune system and the functional capacity of the bone marrow. In the context of CIN, leukopenia, particularly neutropenia, serves as a critical indicator of increased susceptibility to infections. White blood cells, encompassing various cell types including neutrophils, lymphocytes, monocytes, eosinophils, and basophils, play diverse roles in immune defense. Neutrophils, the most abundant type of white blood cell, are the first line of defense against bacterial and fungal infections. They are responsible for migrating to sites of infection, engulfing and destroying invading pathogens. Conditions that affect the bone marrow's ability to produce white blood cells, such as leukemia, aplastic anemia, and certain vitamin deficiencies, can lead to leukopenia. Autoimmune disorders, hypersplenism, and certain infections can cause increased destruction of white blood cells, resulting in leukopenia. Several medications, including chemotherapy, immunosuppressants, and certain antibiotics, can suppress bone marrow function and lead to leukopenia. In the setting of chemotherapy, leukopenia, particularly neutropenia, is a frequent consequence of the myelosuppressive effects of chemotherapeutic agents. These agents target rapidly dividing cells, including cancer cells and hematopoietic stem cells in the bone marrow. The resulting suppression of bone marrow activity can lead to a decrease in the production of all blood cell lineages, including neutrophils. Pre-existing leukopenia in cancer patients can further compound the neutropenic effects of chemotherapy. Patients with leukopenia may have a limited reserve of neutrophils and a diminished capacity to fight infections, making them highly vulnerable to developing CIN and associated complications. The co-existence of anemia and leukopenia in cancer patients can create a synergistic effect, significantly amplifying the risk of CIN and its associated complications. These hematologic abnormalities reflect a compromised bone marrow reserve and a weakened immune system, rendering patients particularly susceptible to the myelosuppressive effects of chemotherapy. Anemia, by

impairing oxygen delivery to the bone marrow, can disrupt hematopoiesis and reduce neutrophil production. Leukopenia, particularly neutropenia, further diminishes the pool of neutrophils available to combat infections. The combination of these factors creates a vulnerable state where patients are at heightened risk of developing CIN and experiencing severe infections. The strong association between anemia, leukopenia, and CIN underscores the critical importance of hematologic monitoring in cancer patients, especially those undergoing chemotherapy. Regular assessment of hemoglobin and leukocyte counts, including neutrophil counts, is essential for identifying patients at increased risk of CIN and implementing appropriate preventive and management strategies. Addressing underlying causes of anemia, such as iron deficiency or vitamin B12 deficiency, can help improve hemoglobin levels and potentially enhance bone marrow function. Granulocyte colony-stimulating factors (G-CSFs) can stimulate neutrophil production and reduce the duration and severity of neutropenia. Prophylactic use of G-CSFs may be considered in high-risk patients with anemia and leukopenia. Patients with anemia and leukopenia should be closely monitored for signs and symptoms of infection, such as fever, chills, cough, and skin rash. Prompt initiation of antibiotics and supportive care can prevent serious complications. Patients should be educated about the risk of CIN and its potential complications. They should be informed about the signs and symptoms of infection and instructed to seek medical attention promptly if they develop any concerning symptoms.[11-13]

While our study identified anemia and leukopenia as strong predictors of chemotherapy-induced neutropenia (CIN), it's equally important to analyze the factors that did not show a significant association. Interestingly, age, nutritional status, breast cancer subtype, and tumor stage did not significantly correlate with CIN incidence in our study population. This unexpected finding challenges some existing assumptions and prompts a deeper exploration of the complex interplay of factors influencing CIN development. Age is often considered a significant risk factor for various treatment-related complications, including CIN. Older patients tend to have decreased physiological reserves, impaired organ function, and a higher prevalence of comorbidities, all of which can contribute to increased vulnerability to adverse effects. However, our study did not find a significant association between age and CIN. Several factors may explain this observation. Firstly, our study population predominantly consisted of relatively younger patients (15-64 years), which may have limited the ability to detect age-related differences in CIN susceptibility. Secondly, the impact of age on CIN may be less pronounced in the context of modern chemotherapy regimens and supportive care measures, which have improved the tolerability and safety of cancer treatment. Furthermore, it's important to recognize that age is not a homogenous entity. Chronological age may not accurately reflect an individual's biological age and overall health status. Factors such as genetics, lifestyle, and comorbidities can significantly influence an individual's physiological resilience and response to treatment, regardless of chronological age. Our findings suggest that while age may be a contributing factor, it may not be a primary determinant of CIN risk. This highlights the need for individualized risk assessment that considers not only chronological age but also other patient-specific factors, such as comorbidities, functional status, and hematologic profiles. Nutritional status is another factor often implicated in CIN risk. Malnutrition can compromise immune function, impair wound healing, and increase susceptibility to infections. However, our study did not find a significant association between nutritional status, as assessed by body mass index (BMI), and CIN incidence. This finding may be attributed to several factors. Firstly, BMI is a crude measure of nutritional status and may not accurately reflect the complex interplay of dietary intake, nutrient absorption, and metabolic processes that contribute to overall nutritional health. Secondly, our study population predominantly consisted of normoweight

individuals, which may have limited the ability to detect the impact of malnutrition on CIN risk. Furthermore, the relationship between nutritional status and CIN is likely more nuanced than simply being underweight or overweight. Specific nutrient deficiencies, such as deficiencies in iron, vitamin B12, and folate, can directly impact hematopoiesis and immune function, increasing vulnerability to CIN. Our findings suggest that while maintaining a healthy weight is important, a more comprehensive assessment of nutritional status, including evaluation of specific nutrient deficiencies, may be necessary to identify patients at increased risk of CIN. Breast cancer is a heterogeneous disease with various subtypes characterized by distinct molecular profiles, clinical behaviors, and treatment responses. Some subtypes, such as triple-negative breast cancer, are known for their aggressive nature and poorer prognosis, often requiring more intensive chemotherapy regimens. It is plausible that the aggressiveness of certain subtypes and the intensity of treatment could influence CIN risk. However, our study did not find a significant association between breast cancer subtype and CIN incidence. This finding suggests that the risk of CIN may be more dependent on individual hematologic profiles and treatment-related factors, such as the specific chemotherapeutic agents used and their dosage, rather than the inherent molecular characteristics of the tumor. This observation has important implications for treatment decision-making. It suggests that the choice of chemotherapy regimen should be primarily guided by factors such as disease stage, hormone receptor status, and HER2 status, rather than concerns about differential CIN risk based on subtype. Tumor stage, which reflects the extent of cancer spread, is a crucial prognostic factor and often influences treatment intensity. Advanced-stage disease may require more aggressive chemotherapy regimens, potentially increasing the risk of myelosuppression and CIN. However, our study did not find a significant association between tumor stage and CIN incidence. This may be because our study included patients with various stages of breast cancer, from early-stage to metastatic disease. The inclusion of patients across different stages may have diluted the potential impact of stage on CIN risk. Furthermore, the relationship between tumor stage and CIN risk is likely complex and multifactorial. While advanced-stage disease may necessitate more intensive chemotherapy, it may also be associated with other factors that can influence CIN susceptibility, such as bone marrow involvement, malnutrition, and impaired organ function. Our findings suggest that while tumor stage is an important consideration in treatment planning, it may not be a primary determinant of CIN risk. Individualized risk assessment should consider not only tumor stage but also other patient-specific factors, including hematologic profiles, comorbidities, and overall health status.[14-16]

Our study delved into the intricate relationship between chemotherapy regimens and the incidence of chemotherapy-induced neutropenia (CIN). Surprisingly, we found no significant difference in CIN occurrence between patients receiving anthracycline-based chemotherapy and those receiving taxane-based chemotherapy. This unexpected finding challenges some preconceived notions and warrants a closer examination of these two prominent chemotherapy classes, their mechanisms of action, and their impact on the delicate balance of hematopoiesis. Anthracyclines, such as doxorubicin and epirubicin, are potent chemotherapeutic agents that have significantly improved outcomes for breast cancer patients. Their efficacy stems from their ability to disrupt DNA replication and repair, ultimately leading to cancer cell death. However, this powerful mechanism of action comes with a price – myelosuppression, a common side effect that can manifest as neutropenia. Anthracyclines intercalate between DNA base pairs, disrupting DNA structure and hindering DNA replication and transcription. Anthracyclines inhibit topoisomerase II, an enzyme essential for DNA unwinding and replication, leading to DNA strand breaks and cell death. Anthracyclines generate free radicals, highly reactive molecules that

can damage DNA and other cellular components, contributing to cell death. While these mechanisms effectively target rapidly dividing cancer cells, they also affect other rapidly dividing cells in the body, including hematopoietic stem cells in the bone marrow. The resulting suppression of bone marrow activity can lead to a decrease in the production of all blood cell lineages, including neutrophils, increasing the risk of CIN. Taxanes, including paclitaxel and docetaxel, are another cornerstone of breast cancer chemotherapy. They exert their anti-cancer effects by targeting microtubules, essential components of the cell's cytoskeleton involved in cell division and intracellular transport. However, like anthracyclines, taxanes also carry the risk of myelosuppression and CIN. Taxanes bind to microtubules and stabilize them, preventing their depolymerization and disrupting the dynamic instability essential for cell division. The stabilization of microtubules leads to mitotic arrest, preventing the separation of chromosomes during cell division and ultimately leading to cell death. While taxanes primarily target microtubules involved in cell division, they can also affect microtubules in other cells, including hematopoietic stem cells. This can disrupt the delicate balance of hematopoiesis, leading to a decrease in neutrophil production and an increased risk of CIN. Given their distinct mechanisms of action, one might expect a difference in CIN incidence between anthracyclines and taxanes. However, our study found no significant difference, suggesting that both classes of agents carry a similar risk of neutropenia. This seemingly paradoxical finding prompts a deeper exploration of the factors influencing CIN susceptibility. The dose and schedule of chemotherapy administration can significantly influence the degree of myelosuppression. While both anthracyclines and taxanes can cause neutropenia, the specific dose and schedule used in our study may have resulted in similar levels of myelosuppression for both classes. Individual patient factors, such as age, nutritional status, comorbidities, and genetic predisposition, can influence susceptibility to CIN. The similar incidence of CIN observed in our study may reflect the influence of these patient-specific factors, which may outweigh the differences in the mechanisms of action of the chemotherapy agents. Our study highlighted the importance of baseline hematologic profiles, particularly anemia and leukopenia, in predicting CIN risk. Patients with pre-existing anemia or leukopenia may be more vulnerable to the myelosuppressive effects of both anthracyclines and taxanes, regardless of the specific mechanism of action. The finding that anthracyclines and taxanes carry a similar risk of CIN has important implications for clinical practice. The extent of cancer spread and the presence of metastases can influence the choice of chemotherapy regimen. The expression of hormone receptors (estrogen and progesterone receptors) on cancer cells can guide the selection of hormonal therapy in conjunction with chemotherapy. The overexpression of human epidermal growth factor receptor 2 (HER2) on cancer cells can indicate the use of targeted therapies, such as trastuzumab, in combination with chemotherapy. By considering these factors, clinicians can optimize treatment strategies and tailor regimens to individual patient needs, rather than focusing solely on concerns about differential CIN risk between anthracyclines and taxanes.[17,18]

Our research findings have significant clinical implications for the management of breast cancer patients undergoing chemotherapy, particularly in the realm of preventing and managing chemotherapy-induced neutropenia (CIN). The identification of anemia and leukopenia as independent predictors of CIN underscores the need for a proactive and vigilant approach to hematologic monitoring and intervention. By translating these research findings into clinical practice, healthcare providers can optimize patient care, minimize the risk of CIN and its associated complications, and ultimately improve treatment outcomes and quality of life. The cornerstone of CIN prevention lies in meticulous hematologic monitoring. Our findings emphasize the importance of baseline and ongoing monitoring of hematologic profiles, particularly hemoglobin and leukocyte counts, in all breast cancer patients undergoing chemotherapy. A

comprehensive blood count should be performed before initiating chemotherapy to establish baseline values for hemoglobin, leukocyte count, and neutrophil count. This baseline assessment serves as a critical reference point for monitoring changes in blood counts during treatment and identifying potential pre-existing hematologic abnormalities. Iron deficiency anemia is a common cause of anemia. Assessing iron status through serum ferritin and transferrin saturation levels can help identify patients who may benefit from iron supplementation to optimize hemoglobin levels before and during chemotherapy. If anemia or leukopenia is detected at baseline, further investigations may be warranted to identify underlying causes, such as vitamin B12 or folate deficiency, chronic kidney disease, or autoimmune disorders. Regular monitoring of complete blood counts throughout chemotherapy is crucial for detecting early signs of myelosuppression and neutropenia. The frequency of monitoring may vary depending on the specific chemotherapy regimen, patient risk factors, and clinical judgment. Patients with pre-existing anemia or leukopenia, or those receiving chemotherapy regimens known for their high myelosuppressive potential, may require more frequent monitoring than those with normal baseline blood counts and lower-risk regimens. Monitoring trends in blood counts over time is essential for identifying gradual declines that may precede clinically significant neutropenia. This allows for early intervention and preventive measures. Early recognition of patients at higher risk of CIN enables timely intervention to mitigate the risk and prevent complications. Our findings support the use of prophylactic and supportive measures, such as granulocyte colony-stimulating factors (G-CSFs) and close monitoring for signs and symptoms of infection. G-CSFs are growth factors that stimulate the production of neutrophils in the bone marrow, accelerating neutrophil recovery and reducing the duration and severity of neutropenia. Prophylactic use of G-CSFs may be considered in high-risk patients, such as those with pre-existing anemia or leukopenia, those receiving highly myelosuppressive chemotherapy regimens, or those with a history of previous episodes of CIN. The decision to use G-CSFs prophylactically should be individualized based on patient risk factors, the specific chemotherapy regimen, and potential side effects of G-CSFs. Patients should be educated about the signs and symptoms of infection, such as fever, chills, cough, sore throat, skin rash, and urinary symptoms. They should be instructed to seek medical attention promptly if they develop any concerning symptoms. Regular monitoring of vital signs, including temperature, heart rate, and respiratory rate, can help detect early signs of infection. If signs or symptoms of infection are present, prompt evaluation and treatment with antibiotics and supportive care are crucial to prevent serious complications, such as sepsis. Patient education and counseling are integral components of CIN prevention and management. By empowering patients with knowledge and understanding, healthcare providers can foster active participation in their care and promote adherence to preventive measures and treatment recommendations. Patients should be provided with a clear and concise explanation of CIN, including its causes, risk factors, potential complications, and management strategies. Patients should understand the importance of regular blood count monitoring and the need to report any concerning symptoms promptly. Patients should be educated about the signs and symptoms of infection and instructed to seek medical attention immediately if they develop any of these symptoms. Patients should be advised on preventive measures, such as hand hygiene, avoiding close contact with sick individuals, and maintaining good nutrition. Patients should be informed about the management of CIN, including the use of G-CSFs, antibiotics, and supportive care. Patients may experience anxiety and fear related to the risk of CIN and its potential complications. Providing emotional support and addressing their concerns is essential. Engaging patients in shared decision-making regarding their care can enhance their sense of control and improve adherence to treatment

recommendations. Developing individualized care plans that consider patient preferences, values, and lifestyle can promote patient satisfaction and improve outcomes. Maintaining open communication and addressing patient questions and concerns can foster trust and facilitate effective collaboration.[19,20]

5. Conclusion

This study investigated the association between hematologic profiles and chemotherapy-induced neutropenia (CIN) in breast cancer patients receiving anthracycline- or taxane-based chemotherapy. We found that anemia (Hb < 12 g/dL) and leukopenia were independent predictors of CIN, regardless of age, nutritional status, breast cancer subtype, or tumor stage. These findings highlight the critical role of hematologic monitoring in identifying patients at higher risk of CIN. Early recognition of these patients allows for timely intervention, such as prophylactic use of G-CSFs and close monitoring for signs and symptoms of infection, which can help minimize treatment disruptions, reduce morbidity and mortality, and improve the overall quality of life for breast cancer patients. Future research should focus on prospective studies with larger sample sizes to confirm these findings and further investigate the complex interplay of factors contributing to CIN.

6. References

1. Staudigl C, Seifert M, Tea M-K, Pfeiler G, Fink-Retter A, Fritzer N, et al. Chemotherapy-induced neutropenia in breast cancer patients receiving sequential anthracycline and taxane chemotherapy: an institutional experience. Cancer Res. 2012; 72(24_Supplement): P1-15-10.
2. Chiarotto JA, Dranitsaris G. Full-dose chemotherapy in early stage breast cancer regardless of absolute neutrophil count and without G-CSF does not increase chemotherapy-induced febrile neutropenia. Support Care Cancer. 2013; 21(10): 2727–31.
3. Tang NLS, Liao CD, Wang X, Mo FKF, Chan VTC, Ng R, et al. Role of pharmacogenetics on adjuvant chemotherapy-induced neutropenia in Chinese breast cancer patients. J Cancer Res Clin Oncol. 2013; 139(3): 419–27.
4. Chang L-L, Schneider SM, Chiang S-C, Horng C-F. Implementing an evidence-based risk assessment tool to predict chemotherapy-induced neutropenia in women with breast cancer. Cancer Nurs. 2013; 36(3): 198–205.
5. Fontanella C, Bolzonello S, Lederer B, Aprile G. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. Breast Care (Basel). 2014; 9(4): 239–45.
6. Lee KH, Kim J-Y, Lee MH, Han HS, Lim JH, Park KU, et al. A randomized, multicenter, phase II/III study to determine the optimal dose and to evaluate the efficacy and safety of pegteograstim (GCPGC) on chemotherapy-induced neutropenia compared to pegfilgrastim in breast cancer patients: KCSG PC10-09. Support Care Cancer. 2016; 24(4): 1709–17.
7. Akpo EIH, Jansen IR, Maes E, Simoens S. Lipegfilgrastim highly cost-effective in reducing chemotherapy-induced neutropenia in breast cancer patients. Eur J Cancer. 2017; 72: S44.
8. Agiro A, DeVries A, Malin J, Fisch MJ. Real-world impact of a decision support tool on colony-stimulating factor use and chemotherapy-induced febrile neutropenia among patients with breast cancer. J Natl Compr Canc Netw. 2018; 16(2): 162–9.
9. Aapro M, Krendyukov A, Krivtsova N, Gascon P. Treatment patterns and outcomes in patients with breast cancer receiving biosimilar filgrastim for prophylaxis of chemotherapy-induced/febrile neutropenia: Results from the MONITOR-GCSF study. Eur J Cancer. 2018; 92: S53.

10. Kahan Z, Grecea D, Smakal M, Tjulandin S, Bondarenko I, Perjesi L, et al. Efficacy and safety of RGB-02, a pegfilgrastim biosimilar to prevent chemotherapy-induced neutropenia: results of a randomized, double-blind phase III clinical study vs. reference pegfilgrastim in patients with breast cancer receiving chemotherapy. BMC Cancer. 2019; 19(1): 122.
11. Weycker D, Silvia A, Hanau A, Lamerato L, Richert-Boe K, Kaur M, et al. Risk of chemotherapy-induced febrile neutropenia (FN) in patients with metastatic cancer of the breast or other sites not receiving colony-stimulating factor prophylaxis (CSF) in US clinical practice. Cancer Res. 2020; 80(4_Supplement): P2-08-24.
12. Wuerstlein R, Harbeck N, Grischke E-M, Forstmeyer D, von Schumann R, Krabisch P, et al. Protroca: a noninterventional study on prophylactic lipegfilgrastim against chemotherapy-induced neutropenia in nonselected breast cancer patients. Breast Care (Basel). 2021; 16(1): 50–8.
13. Cobb PW, Moon YW, Mezei K, Láng I, Bhat G, Chawla S, et al. A comparison of eflapegrastim to pegfilgrastim in the management of chemotherapy-induced neutropenia in patients with early-stage breast cancer undergoing cytotoxic chemotherapy (RECOVER): a Phase 3 study. Cancer Med. 2020; 9(17): 6234–43.
14. Blayney DW, Huang L, Mohanlal RW. A confirmatory trial to demonstrate superiority of the plinabulin+pegfilgrastim (PLIN/PEG) combination versus standard of care pegfilgrastim for the prevention of chemotherapy-induced neutropenia (CIN) in breast cancer (BC) patients (PTS). Cancer Res. 2021; 81(4_Supplement): OT-06-02.
15. Ong SS, Ho PJ, Khng AJ, Lim EH, Wong FY, Tan BK-T, et al. Association between breast cancer polygenic risk score and chemotherapy-induced febrile neutropenia: Null results. Cancers (Basel). 2022; 14(11): 2714.
16. Moon YW, Kim SK, Lee KS, Lee MH, Park YH, Park KH, et al. Eflapegrastim versus pegfilgrastim for chemotherapy-induced neutropenia in Korean and Asian patients with early breast cancer: Results from the two phase III ADVANCE and RECOVER studies. Cancer Res Treat. 2023; 55(3): 766–77.
17. Zha X, Wang J, Xu Y, He J, Wang Y, Zhang W, et al. A prospective, randomized, controlled clinical trial comparing different PEG-rhG-CSF administration times to treat chemotherapy-induced neutropenia and febrile neutropenia in early breast cancer. Cancer Res. 2024; 84(9_Supplement): PO4-20-02.
18. ELKasar AO, Hussien FZ, Abdel-Hamied HE, Saleh IG, Mahgoup EM, El-Arabey AA, et al. Effect of lithium on chemotherapy-induced neutropenia in Egyptian breast cancer patients; a prospective clinical study. Cancer Chemother Pharmacol. 2024; 93(6): 541–54.
19. Morecroft R, Logothetics CN, Tarnawsky SP, Davis AA. Chemotherapy-induced neutropenia management in a patient with metastatic breast cancer and Shwachman-Diamond syndrome (SDS): a case report. Transl Breast Cancer Res. 2024; 5: 26.
20. Zhang Q, Wang Z, Yao W, Wang S, Zhang G, Chen J, et al. A randomized, multicenter phase III Study of once-per-cycle administration of efbemalenograstim alfa (F-627), a novel long-acting rhG-CSF, for prophylaxis of chemotherapy-induced neutropenia in patients with breast cancer. BMC Cancer. 2024; 24(1): 1143.