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Assessment of Hematological Parameters Alteration and Associated Factors among Breast Cancer Patients Receiving Chemotherapy at Worabe Comprehensive Specialized Hospital, Worabe, Central Ethiopia

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This is to certify that the thesis prepared by Abdilaziz Nassir Hussen, entitled: "Assessment of Hematological Parameters alteration and Associated Factors among Breast Cancer Patients receiving Chemotherapy at Worabe Comprehensive Specialized Hospital, Worabe, Central Ethiopia", and submitted in partial fulfillment of the requirements for the Master of Science degree in Clinical Laboratory Sciences (Hematology and Immunohematology), complies with the regulations of the University and meets the accepted standards of originality and quality.

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Abbreviations

AAU	Addis Ababa University,
BAS	Basophil
BMI	Body Mass Index
CBC	Complete Blood Count
CMHS	College of Health Science
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediaminetetraacetic Acid
EOS	Eosinophil
GIT	Gastrointestinal Tract
HCT	Hematocrit
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
LYM	Lymphocyte
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
NUT	Neutrophil
OPD	Outpatient Department
PLT	Platelet
RBC	Red Blood Cell
RDW	Red cell Distribution Width
SBRT	Stereotactic Body Radiation Therapy
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
WBC	White Blood Cell
WCSH	Worabe Comprehensive Specialized Hospital
WHO	World Health Organization

Abstract

Background: Breast cancer is the most common cancer that forms tumors in the tissues of the breast and is the leading cause of cancer deaths in women. Chemotherapy, the most effective treatment for breast cancer, targets not only cancer cells but also rapidly dividing healthy cells, including the bone marrow cells. These bone marrow cell damages can reduce the quality of life of the patient.

Objective: To determine hematological parameter alteration and associated risk factors in breast cancer patients undergoing chemotherapy at Worabe Comprehensive Specialized Hospital from December 2023 to December 2024, Worabe, Central Ethiopia.

Methods: A cohort study design with primary and secondary data was implemented in breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital. After receiving consent, patients who met the inclusion and exclusion criteria were identified. Socio-demographic and clinical information were gathered by using a structured questionnaire and from the patient's file. About 3-4 ml of blood was collected and analyzed by using a Sysmex 550 hematological analyzer throughout four chemotherapy cycles. The data were entered and analyzed using SPSS version 27. The data were summarized and described by using descriptive statistics. Non-parametric tests (Friedman, Mann-Whitney U, and Kruskal-Wallis with Bonferroni correction) were employed for statistical analysis, due to the non-normal distribution of the data.

Result: This study of 43 female breast cancer patients revealed significant decreases in median values for RBC count (4.70 to 4.27 $\times 10^6/\mu l$), hemoglobin (13.60 to 12.60 g/dl), hematocrit (39.6 to 36.7%), MCH (29.3 to 28.9 pg), and MCHC (34.3 to 33.3 g/dl), but the RDW and MCV significantly rose. While the WBC parameters, including total WBC, neutrophil, and lymphocyte counts, also decreased significantly. The platelet counts rose insignificantly. The socio-demographic like residence and clinical factors, such as stage of cancer and age, were affect RBC count, hemoglobin level, MCV, and MCH during chemotherapy. The total WBC and platelet count during the treatment of chemotherapy were affected by metastasis of the cancer, occupation, and stage of the cancer, but many findings weren't significant after Bonferroni correction.

Conclusion: This study demonstrates that breast cancer chemotherapy can significantly impact most hematological profiles, including RBC count, hemoglobin, hematocrit, total WBC count, neutrophil count, and lymphocyte count. The platelet count shows an insignificant increment. Stage and metastasis of the cancer and residence of the patient increase the effect of chemotherapy.

Key words: Hematological parameter, Breast cancer, Chemotherapy

1 Introduction

1.1 Background

In normal physiological conditions, cells in the body are capable of dividing and multiplying when the body requires growth and repair. When cells are aged or damaged in different conditions, they will be destroyed and replaced by new cells(1). Cancer is a mutagenic disease with many etiological factors that can arise from any cell type and organs. The disease is characterized by some body cells growing out of control, which can lead to invasion or spread to other body areas(2).

Tumor cells are transformed into malignant ones through a multistage process influenced by genetic factors and external factors like chemical carcinogens, air pollution, asbestos, tobacco smoke, and arsenic(3). Reducing the risk of certain cancers can be achieved through lifestyle changes like quitting smoking, maintaining a healthy weight, and avoiding processed meat and sunlight (4). In terms of new cases, the most prevalent cancer kinds according to WHO statistics in 2020 are lung, breast, colon and rectum, prostate, skin, and stomach; in terms of new deaths, lung, colon and rectum, liver, stomach, and breast cancers(5).

Breast cancer is the major type and leading cause of cancer deaths among women, especially in low- and middle-income nations, despite tremendous advancements in the diagnosis and survival rates of breast cancer. In many African nations, the prevalence of breast cancer is rising, yet there are still remarkably few programs in place to control it (6, 7, 8).

The breast is composed of three main components: the lobules, which are the milk-producing glands; milk ducts(tubes) that transport milk to the chest or abdomen; and the connective tissue that surrounds and holds everything together(9). Breast cancer is a type of cancer that develops in the cells of the breast and can occur in both men and women, although it is much more common in women(10). It usually begins in the inner lining of milk ducts or the lobules that supply them with milk. If the cancer is not treated early, it may disseminate to other areas of the body and increase the risk of life-threatening conditions. The common varieties of breast cancer encompass ductal carcinoma in situ, invasive ductal carcinoma, and invasive lobular carcinoma. The risk factors for developing breast cancer include genetic mutations like breast cancer gene (BRCA1

and BRCA2), family history, age, exposure to radiation, hormonal influences, and lifestyle factors such as alcohol consumption and obesity(6, 11, 12).

The symptoms of breast cancer can vary, but often include a lump in the breast, alteration in size or shape of the breast, dimpling of the skin, nipple discharge, or pain in the breast. Diagnosis typically involves a combination of physical exams, mammograms, ultrasounds, biopsies, and sometimes magnetic resonance imaging(13). Treatment options for breast cancer depend on the type and stage of the disease, including surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy, either independently or in combination. Early detection and treatment are crucial in improving the prognosis and survival rates for those affected by breast cancer(14, 15).

Chemotherapy is a common treatment for breast cancer, especially in aggressive cases, when the cancer has spread, or if there's a high risk of recurrence(10). The goal is to destroy cancer cells, shrink tumors, and prevent their spread or returning. There are different types of chemotherapy: neoadjuvant before surgery, adjuvant after surgery, and metastatic for cancer that has spread to other parts of the body. Various types of chemotherapy drugs are used to treat breast cancer, such as anthracyclines like doxorubicin (Adriamycin), taxanes like paclitaxel (Taxol), alkylating agents like cyclophosphamide, and antimetabolites like 5-fluorouracil. Chemotherapy can be given orally or intravenously in cycles to allow the body to recover. The treatment plan depends on the type and stage of breast cancer, as well as the patient's overall health status. The treatment is given either single drug or combination of more than one drug. Using a combination of drugs increases the effectiveness of treatment by targeting different phases of the cell reproduction cycle and reducing resistance of body to specific drugs (16, 17, 18).

The effectiveness of chemotherapy depends on factors like the type of breast cancer, its stage, and how the cancer cells respond to the treatment. It can improve survival rates and reduce recurrence risk, especially in aggressive breast cancers. It is often part of a comprehensive treatment plan that may include surgery, radiation therapy, hormonal therapy, and targeted therapy depending on the specific characteristics of the breast cancer(19, 20).

The chemotherapy drugs used in breast cancer can not only destroy cancer cells but also affect bone marrow, GI tract, and hair follicles(21). Which leads to undesirable adverse effects such as fatigue, nausea, hair loss, and an increased risk of infection. Other common side effects include

mouth sores, loss of appetite, and changes in nails and skin. Depending on the drugs used and their dosage, it may cause long-term effects like infertility, early menopause, and a higher risk of other cancers (22, 23, 24).

Various studies show that chemotherapy has significant impacts on hematological parameters due to its myelosuppressive effects. It affects bone marrow by depleting hematopoietic stem cells, inhibiting DNA synthesis, and disrupting microtubule function. This causes a decrease in hemoglobin, platelets, and leukocyte levels. Chemotherapy also causes loss of immunity and anemia in patients, suppressing immune cells and leading to opportunistic infections(25, 26).

Anemia is the most common side effect of chemotherapy, due to a decrease in RBC production, which can lead the patient for fatigue, shortness of breath, and weakness. Thrombocytopenia and Leukopenia, particularly neutropenia, are other common complications of chemotherapy. These conditions make the patient susceptible to various infections and bleeding problems(24, 27, 28).

Monitoring and managing these conditions are crucial for optimizing treatment outcomes, ensuring patient safety, and minimizing the risk of morbidity and mortality. Supportive treatments, such as blood transfusions, growth factor injections (e.g., erythropoietin for anemia, G-CSF for neutropenia), and platelet transfusions, are often used to mitigate the risks associated with chemotherapy-induced hematological abnormalities(29, 30).

A Complete Blood Count is a standard laboratory test to assess overall health status and helps in identifying various medical issues, including anemia and infections. It provides a snapshot of health status and is valuable in routine checkups and monitoring patients undergoing chemotherapy. The use of CBC during chemotherapy is crucial for monitoring blood health, platelet count, and ensuring normal red and white blood cell function. It assists in detecting anemia and the risk of infection, guiding treatment decisions, and effectively managing side effects. CBC provides essential information about WBCs, RBCs, and platelets, and assists health professionals in diagnosing complications of chemotherapy in breast cancer and other diseases.

Hematological parameters like RBC count, hemoglobin, hematocrit, MCV, MCHC, total WBC count, and neutrophil count significantly declined after being treated by chemotherapy compared to baseline. The platelet count increases or decreases after treatment(24, 28, 31).

1.2 Statement of the problem

Breast cancer is one of the most prevalent malignancies worldwide, and significant contribution to morbidity and mortality among women. It is affecting about 1 in 8 females. 2.3 million people were newly diagnosed with breast cancer, and 685,000 people died by breast cancer in 2020. In low- and middle-income countries, the burden of breast cancer is rising, facing challenges such as late-stage diagnosis, limited healthcare access, and high mortality rates. High-income countries have the highest incidence, with a lower mortality rate due to early detection and better access to treatment.

Despite having historically lower incidence rates compared to high-income countries, breast cancer cases in Africa are rising at an alarming rate. Based on WHO data in 2020, about 198,000 people were newly diagnosed in breast cancer, and 91,000 people died by breast cancer in Africa. The mortality rate is disproportionately high compared to other regions, primarily due to late-stage diagnosis and limited access to effective healthcare and treatment options. Several factors contribute to the burden of breast cancer in Africa, including a lack of awareness about symptoms, shortage of specialized healthcare facilities, trained medical personnel, and resources for cancer treatment, such as chemotherapy and radiation therapy (32, 33).

Breast cancer has a significant socioeconomic impact in Africa, particularly in countries like Ethiopia. It leads to financial problems and a decrease in productivity. High treatment costs, lack of insurance, and limited healthcare infrastructure exacerbate the problem, pushing many families into poverty. The disease also results in a loss of income as women are unable to work during treatment, further increasing dependency. Stigma and a lack of awareness surrounding breast cancer hinder early diagnosis and treatment, contributing to poor outcomes. In Ethiopia, patients, especially those from low-income backgrounds, struggle to afford treatment and travel to specialized centers. To address these challenges, there is a need for improved public health strategies, early detection initiatives, and expanded cancer care infrastructure. Empowering women with access to healthcare services is crucial in the fight against breast cancer in Africa (34, 35, 36).

Breast cancer has overtaken cervical cancer as the most frequently diagnosed cancer in women in sub-Saharan African countries. Its burden is expected to rise due to urbanization-related risk factors. In Ethiopia, the burden of breast cancer has been increasing, with a growing number of

patients requiring treatment. In 2020, Ethiopia reported more than 15,000 new cases of breast cancer, with over 7,000 deaths, according to the WHO. It is about 33% of cancers in women and 23% of both sexes in Ethiopia. Most patients present with advanced disease, with 67% having locally advanced cancer and 25% having metastatic cancer. All these factors result in unsatisfactory treatment outcomes(37, 38, 39).

A key factor for increasing the burden of breast cancer in Ethiopia is its late-stage diagnosis. Many women present with advanced-stage breast cancer due to limited awareness of the disease, cultural taboos, and insufficient access to health education. This delay in seeking medical care often results in poor treatment outcomes, as early-stage breast cancer is more treatable. Moreover, Ethiopia's healthcare system faces significant challenges, such as a shortage of cancer specialists, inadequate diagnostic facilities, and limited availability of treatment options like surgery, chemotherapy, and radiation therapy(40, 41).

Chemotherapy is one of the most common and effective therapeutic approaches used in the management of breast cancer. However, it is known to cause various adverse effects, including alterations in hematological parameters. Hematological parameters, such as red blood cells, white blood cells, hemoglobin, and platelets, play vital roles in the body's immune response and overall function. The drugs deplete hematopoietic stem cells in the bone marrow, inhibiting microtubule, protein, and DNA synthesis. This leads to cell death, resulting in decreased levels of hemoglobin, platelets, and leukocytes, which can lead to complications such as anemia and leukopenia thrombocytopenia. Anemia is one of the most common side effects of breast cancer treatment, which decreases the effectiveness of chemotherapy drugs on malignant cells and complicates breast cancer management. Neutropenia is a decreased number of neutrophils in the blood, a higher risk for dangerous infection, and the most serious adverse effect of chemotherapy. These complications not only affect the patient's quality of life but can also lead to treatment delays or discontinuation, further exacerbating the disease prognosis and mortality directly or indirectly(27, 42, 43).

Chemotherapy can also affect RBC parameters like MCV, MCH, and MCHC values in breast cancer patients, which leads to a decrease in RBC count and hemoglobin levels. Hematological disorders such as anemia, thrombocytopenia, and leucopenia are associated with chemotherapy-induced side effects, which affect patients' quality of life. The incidence of bleeding in breast

cancer patients can range from mild to severe. Severe bleeding in the presence of thrombocytopenia or other clotting disorders, potentially leading to serious morbidity or death. Thrombocytopenia is a common problem experienced by breast cancer patients, often due to chemotherapy. The total leukocyte count and the relative count of neutrophils, lymphocytes, eosinophils, monocytes, and basophils in breast cancer-treated patients show a decrease. Chemotherapy drugs damage neutrophils in breast cancer patients, potentially leading to neutropenia. Chemotherapy-induced myelosuppression of hematopoietic cells is a significant concern, as it is associated with 8.5% of all cancer deaths(27, 44, 45).

Despite the widespread use of chemotherapy in breast cancer treatment in Ethiopia, there is limited information on its impact on the hematological profile of patients. Moreover, associated risk factors such as age, stage of cancer, and the type of chemotherapy regimen used may further contribute to these hematological changes, yet these have not been adequately studied in the local context. Understanding these alterations and their associated factors is crucial for improving patient management, minimizing complications, and enhancing treatment outcomes.

Therefore, this study aims to assess the hematological parameters and associated factors among breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital. This research is critical to filling the knowledge gap, providing evidence-based insights that could guide clinical practices in managing the adverse effects of chemotherapy, and improving patient care in Ethiopia

1.3 Significance of the study

Chemotherapy has common adverse effects on hematological parameters like hemoglobin, white blood cells, and platelets, which are crucial for monitoring breast cancer patients' health. It may lead to a patient having a more complicated condition or death. Understanding these changes will allow healthcare providers to better manage these side effects, ultimately improving patient outcomes. However, there is limited research conducted on the effect of chemotherapy on the hematological profile of breast cancer patients in the study area. The prospective effect of this study for patients will improve treatment progression and reduce the adverse effects of the treatment. It also gives a clue for healthcare providers to assess the hematological status of breast cancer patients at regular intervals. This research meets with global healthcare standards and serves as a reference for future studies. Ultimately, contributing to enhanced care and reducing the burden of chemotherapy-induced hematological profile alterations. It can support the development of treatment guidelines for more effective disease management. This study will add more evidence for researchers and will be an additional input for the Ministry of Health, its partners, and policymakers.

2 Literature review

Chemotherapy is a cancer treatment that uses one or more anticancer drugs to cure the cancer, prolong life, or reduce symptoms. However, it causes damage in the bone marrow, which is a source of pluripotent and multipotent hematopoietic stem cells and most hematological parameters such as RBC, WBC, and platelets. This can lead to complicated cases such as severe anemia, thrombocytopenia, and neutropenia in patients (46, 47, 48)

Anemia complicates breast cancer treatment. It causes fatigue, which is one of the most common side effects of cancer treatment. It may also make chemotherapy drugs less effective against malignant cells. Neutropenia is considered the most serious side effect of chemotherapy and usually causes doctors to reduce the drug dose or limit drug administration, often leading to treatment failure. The number of neutrophils in the blood decreases, increasing the risk of dangerous infections. Thrombocytopenia increases the risk of bleeding and may lead doctors to reduce the dose of chemotherapy drugs, which in turn affects treatment outcomes (49, 50).

Several studies have proven this statement; for instance, a retrospective observational study conducted on comparison of hematological parameters along with the effect of radiotherapy and chemotherapy in different stages of breast cancer in Tamil Nadu, India by Kumutha et al on 2021 shows that the patients who undertook chemotherapy a significant decline in hemoglobin, RBC, neutrophils, lymphocytes and platelets, the mean values are 9.83, 3.63, 42.20, 26.50 and 1.30 respectively. The study also describes that hematological parameters were expressed to decline within the stage of the cancer. The hemoglobin values were decline from stage 1(10.05g/dl) to stage 4(9.25g/dl), total leukocyte counts from Stage1 (5.25×10^3 cell/μl) to Stage 4(4.57×10^3 cell/μl), neutrophil counts were decline from Stage 1 (45.20%) to Stage 4(43.20%) and the lymphocyte counts from Stage 1(24.87%) to Stage 4(21.50%). RBC counts were found to be higher at Stage 2(3.70×10^6 cell/μl), and the lowest at Stage 4(3.20×10^6 cell/μl). But the maximum platelet count was shown on Stage 3(159×10^3 cell/μl) and the lowest count at Stage 2(148×10^3 cell/μl). The findings of this study show that hematological parameters were declining with respect to stages of the breast cancer(51).

A retrospective cohort study conducted by Dorel et al. in 2020 on the comparative hematological profiles of dose-dense versus regular anthracycline-based neoadjuvant chemotherapy in non-

metastatic breast cancer patients in Bucharest, Romania. The study comprised 168 participants. Findings revealed a 15% reduction in hemoglobin levels following the completion of three cycles. Initially, the mean corpuscular volume decreased, but it later increased during the chemotherapy treatment. In contrast, the red blood cell count showed a persistent decline, while platelet counts increased. The neutrophil count within the white blood cell analysis remained largely unchanged, whereas lymphocyte counts showed a notable decrease(52).

A study conducted by Shrivastava et al. in 2016 in Uttar Pradesh, India, employed a comparative cross-sectional design to evaluate hematological parameters and the effect of chemotherapy and radiotherapy on different stages of breast cancer. The results demonstrated a significant decrement in the red blood cell counts, hemoglobin levels, and lymphocyte count after receiving chemotherapy(53).

A prospective cross-sectional study, conducted by Salako et al., was performed at the Lagos University Teaching Hospital in Lagos, Nigeria, between July 2017 and July 2019. In this research, 113 female breast cancer patients were involved to investigate the occurrence of chemotherapy-induced neutropenia and febrile neutropenia within this tertiary healthcare facility. Among the participants of this study 31.9% showed neutropenia. Neutropenic episodes were observed across all chemotherapy treatments, with severity categorized into mild, moderate, and severe cases. Notably, the incidence of neutropenia demonstrated a decreasing trend as chemotherapy cycles progressed, with a higher frequency recorded after the initial treatment and a lower frequency in subsequent cycles. Factors associated with the risk of developing neutropenia include increasing age and presence of bone metastasis(54).

A longitudinal study was conducted by Storph et al. on Ghana in the female surgical ward and laboratory unit of the Cape Coast Teaching Hospital, from May 2016 to February 2017, to evaluate the Effect of Chemotherapy on Clinical, Hematological, and Biochemical profiles in Breast Cancer Patients. The study, involving 51 participants, most of the study participants showed insignificant mean values of hematological parameters (hemoglobin, platelet, and WBC) before the first dose. After the second dose, all the hematological parameters of participants remained normal except for invasive ductal carcinoma patients who had 60% low hemoglobin and WBC. After the 3rd cycle, most of the participants recorded insignificant normal hematological parameters. Though

manifested insignificantly, the majority of the participants had low WBC, normal platelet levels, and normal or low hemoglobin levels(43).

A hospital-based comparative cross-sectional study design was conducted by Abiye et al. from March to November 2022 on the Effects of Adriamycin-Cytoxan chemotherapy on hematological and electrolyte parameters among breast cancer patients in Black Lion Specialized Teaching Hospital and Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. The study compared treated and untreated patients, finding that untreated patients had higher total WBC and lymphocyte counts, but lower eosinophil counts. Hemoglobin, hemoglobin, and HCT values were higher in untreated patients, while PLT and PCT values were lower in treated patients(22).

Another Hospital-based case-control study was done at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, by Fatuma Hassen et al. from May 2018 to June 2019 to assess Socio-demographic and Hematological Determinants of Breast Cancer in a Tertiary Health Care and Teaching Hospital on 230 cases and 230 controls participant. The study found that the mean and standard deviation of hemoglobin, red blood cells, and packed cell volume in cases decreased compared to controls. The mean platelet count was higher in cases, and overall MCV, MCH, and MCHC values were lower in cases compared to controls. The mean counts of neutrophils, lymphocytes, monocytes, and eosinophils were significantly higher in cases(31).

A retrospective cohort study was undertaken by Wondimneh et al. to compare hematological profile changes in pre- and post-chemotherapy treatment of cancer patients who attended Ayder Comprehensive Specialized Hospital in 2019. The mean differences of hematological profiles between pre-chemotherapy and post-chemotherapy were WBC 2.44×10^3 cell/μl, RBC 0.6×10^6 cell/μl, hemoglobin 0.63 g/dl, HCT 2.12%, PLT 22.2×10^3 cell/μl, NUT 2.19%, and LYM 2.88%. Chemotherapy leads to a reduction in WBC count, causing cancer patients to develop infections due to the suppression of hematopoietic stem cells, crucial for WBC proliferation. The reduction of RBC count in patients' post-chemotherapy may be due to ineffective erythropoiesis, a condition characterized by decreased renal production of erythropoietin. Chemotherapy may have damaged megakaryocytic progenitors during the early phases of development, which would explain the decrease in platelet count after treatment(24).

Another retrospective cohort study was conducted by Aynalem, et al. at the University of Gondar Comprehensive Specialized Hospital Cancer Treatment Center on hematological abnormalities

before and after initiation of cancer treatment among breast cancer patients in 2021 hemoglobin concentration before and after treatment was decreased by 1.56g/dl, the white blood cell (WBC) count by 0.33×10^3 cell/µl, the platelet count was 19×10^3 cell/µl. The study shows that red blood cell parameters like RBC count, HCT, hemoglobin, and MCV decrease during breast cancer treatment, while red cell distribution width increases, indicating increased anemia. The high proportion of microcytic cells suggests cell hemolysis(27).

These results overall confirm that chemotherapy hurts hematological indicators in breast cancer patients, hence emphasizing the necessity of ongoing monitoring and supportive measures to control these toxicities and preserve treatment efficacy.

Breast cancer is one of the major public health issues in Ethiopia. In the study area, not enough research was conducted and published about the consequences of chemotherapy on the hematological parameters of breast cancer patients. Most of the literature reviews above implied that chemotherapy affects most of the hematological parameters. Thus, how chemotherapy further aggravates the situation is a research concern, to which this study tries to contribute.

3 Hypothesis

3.1 Null Hypothesis

Chemotherapy has no significant effect on hematological parameters alteration among breast cancer patients.

4 Objectives

4.1 General objectives

- ✓ To determine hematological parameters alteration and associated factors among breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital from December 2023 to December 2024

4.2 Specific objectives

- ✓ To investigate alteration of hematological parameters in breast cancer patients treated with chemotherapy at WCSH from December 2023 to December 2024
- ✓ To determine the factors associated with hematological alteration during chemotherapy treatment at WCSH from December 2023 to December 2024

5 Methods and Materials

5.1 Study area

The study was conducted at Werabe Comprehensive Specialized Hospital, Central Ethiopia Region, Siltie zone, Werabe town. Werabe town is located 172 km south of Addis Ababa and 60 km north of Hosanna.

The WCSH was established on 29th November 2014. During the study period, there were over 1148 employees. With these around 658 clinical are employees. The oncology department, established in 2020, employs a multidisciplinary team consisting of one senior oncologist, two general practitioners, three pharmacists, and six nurses.

The hospital provides services to outpatient, emergency (adult & pediatric), inpatient, ICU, emergency gynecology, general surgery, obstetrics and gynecology surgery, orthopedics, urology, oncology, psychiatry, neurosurgery, neurology, dialysis, internal medicine, radiology services (CT-scan, x-ray, MRI, ultrasound, echocardiography, endoscopy).and laboratory services including pathology, biopsy and culture(55).

5.2 Study design and study period

5.2.1 Study design

A cohort study design with primary and secondary data was conducted.

5.2.2 Study period

The study was conducted from December 2023 to December 2024.

5.3 Population

5.3.1 Source population

All breast cancer patients who were attending the Oncology unit of Worabe Comprehensive Specialized Hospital.

5.3.2 Study population

All breast cancer patients who were treated with chemotherapy at the Oncology Unit of WCSH from December 2023, to December 2024 and fulfilling the eligibility criteria of the study.

5.4 Inclusion and exclusion criteria

5.4.1 Inclusion criteria

- ❖ All female breast cancer patients who received chemotherapy for four cycles at the WCSH oncology unit between December 2023 and December 2024.
- ❖ Patients who had initiated chemotherapy before the study period but had not completed four cycles of treatment, if they had complete medical records.

5.4.2 Exclusion criteria

- ❖ Patients who finished chemotherapy before the study period.
- ❖ Patients who suffered from mental health and hearing problems.
- ❖ Patients with comorbid diseases like HIV, TB, DM, and pregnant women.

5.5 Study variables

5.5.1 Dependent variables

- ✓ Hematological parameters like Red blood cells, hematocrit, hemoglobin, white blood cells, neutrophil, lymphocyte, and platelet

5.5.2 Independent variables

- ✓ Demographic variables: age, marital status, educational level, occupation
- ✓ Disease-related variable: stage and metastasis of cancer
- ✓ Cycle of chemotherapy drugs
- ✓ Baseline hematological parameters

5.6 Sample size determination and Sampling method

5.6.1 Sample size determination

The required data were collected from 43 breast cancer patients attending the oncology unit of WCSH and receiving chemotherapy from December 2023 to December 2024. The sample was calculated using G*power statistical software by considering assumptions of $\alpha=0.05$(95% CI), power($1-\beta$) =80%, an effect size (f) of 0.25, a correlation among repeated measurements of 0.3, and a number of measurements of 5. The result was 37, and the final sample size after adding a 15% dropout rate, 37+6 was 43.

5.6.2 Sampling method

A convenient non-probability sampling technique was implemented.

5.7 Measurement and Data Collection

5.7.1 Data collection procedure

After receiving consent, identified patients who met the inclusion and exclusion criteria. Socio-demographic information was gathered using a structured, pretested questionnaire and from the patient's file. The questionnaires included demography-related questions and clinical-related questions to be obtained by interviewing the patients and from their history. About 3-4 ml of blood was collected for complete blood count using an EDTA test tube. Patients were followed until the end of their four cycles of chemotherapy.

5.8 Laboratory analysis

By using antiseptics to clean the puncture site, 3-4 ml of blood samples were collected in EDTA anticoagulant tubes and labeled with the patient's name and medical record number to ensure accurate traceability, then gently mixed to ensure uniform distribution of cells. After inserting tubes into the Sysmex XN-550 hematology analyzer, the machine takes about 88 microliters of blood, dilutes it, and prepares it for analysis. The sample is split up into various portions, each one assigned to a particular parameter or test.

Principles

The Sysmex XN-550 hematology analyzer generates an accurate and precise hematological profile result by using a highly automated and efficient approach. It utilizes various technologies, including flow cytometry, fluorescence, and impedance, to ensure comprehensive analysis, accurate results, and reliable detection of anomalies in blood samples.

Flow cytometry

In a fluorescence flow cytometry analysis, cells are stained with various specific fluorescent dyes that can identify different components in the cell, such as nucleic acids or other proteins. When the marked cells are passed through a laser beam and the fluorescence is released, the detector senses and measures it. Use this for counting and differentiation of WBC, RBC, and Platelets.

The analyzer detects not only fluorescence, but also forward and side light scatters. The forward scatter tells about the size of the cell, and the side scatter about internal characteristics or granularity of cells. These scattered light assists in identifying various white blood cells and atypical cells.

Impedance Technology

The XN-550 hematology analyzer uses electrical impedance technology in addition to Flow cytometry for counting cells. When a cell passes through a small opening with an electrical current, it changes the resistance. Each little change means one cell has gone by. So, this method is mostly used for counting RBCs and platelets.

Hydrodynamic focusing

The hydrodynamic focusing makes all cells go to the detection area in a single line, like a queue. A sheath fluid wraps around the blood sample, making it easier for the cells to line up nicely. It helps to count cells more accurately and lowers the chances of coincidences, which is when many cells pass by the detector at once.

Optical Fluorescent Platelet Counting

When counting platelets, the analyzer combines optical detection with fluorescence techniques. It mixes in fluorescent dyes that stain the platelets and measures their fluorescence intensity. Similarly, the analyzer uses fluorescent staining to find reticulocytes. The intensity of fluorescence shows how much RNA the cells present. This info helps identify and count reticulocytes effectively.

For hemoglobin measurement, the XN-550 uses the sodium lauryl sulfate (SLS) method. SLS lyses red blood cells and binds to hemoglobin to form a stable complex that is measured photometrically, providing accurate hemoglobin values without lipid interference.

Finally, the analyzer provides information about all types of WBCs: neutrophils, lymphocytes, monocytes, eosinophils, and basophils. This is accomplished through a combination of impedance, fluorescence, and scattered light to create a detailed leukocyte profile.

5.9 Data Quality Assurance

In this study, clinical data were collected directly from patients in the oncology ward. This process included reviewing their history sheets to gather information. Blood samples were collected and analyzed according to standard operating procedures to ensure accuracy and reliability. All materials used in sample collection and analysis were rigorously tested to confirm proper functionality before use. The completion of the questionnaire was monitored and reviewed daily. Quality control measures were implemented in three key phases.

In the pre-analytical phase, the right amount of blood sample was collected by following the correct procedures of venipuncture to avoid hemolysis, clotting, or contamination. Registered the date and time of sample collection and labeled with a unique identification (medical recording number). The sample was transported to the laboratory under appropriate conditions by avoiding excessive shaking and prolonged exposure to extreme temperatures, which can affect the sample's quality. Before the analysis, blood samples were properly mixed to prevent clot formation or cell settling.

During the analytical phase, a quality control sample was run and verified. The sample was processed under the standard operating procedure and machine manual, guaranteeing that all safety procedures were followed.

In the post-analytical phase, cross-checking the results with patient history and interpreting the results was made based on the patient’s condition and chemotherapy regimen. The data entry was accurately ensured and verified.

5.10 Data analysis and interpretation

The data were entered into SPSS version 27 for analysis. Descriptive statistics were summarized using frequencies and percentages. As the data were not normally distributed by the Shapiro-Wilk test, the median and interquartile range (IQR) were used. Figures and tables were used to present the results. Statistical significance was determined using the p-value. The Friedman test was used to assess the effect of chemotherapy across cycles. Distributional differences in hematological parameters across categories of socio-demographic and clinical factors were examined using the Mann-Whitney U test for comparisons between two groups and the Kruskal-Wallis H test for comparisons among multiple groups, followed by Bonferroni correction for multiple comparisons.

5.11 Operational definitions

Hematological profiles are quantifiable blood parameters that may be used for monitoring and identifying certain physiological and pathological conditions.

Breast cancer is disease condition, characterized by an abnormal proliferation of breast ductal and lobular cells.

Chemotherapy is a treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic drugs.

Breast cancer chemotherapy is the drugs (Adriamycin (doxorubicin)) used to treat breast cancer for the first four cycles

Hematological parameters of pre-chemotherapy (baseline) refer to laboratory results of hematological parameters at the time of cancer diagnosis before starting treatment.

Chemotherapy cycle is the time interval between one round of treatment and until start of the next round, typically spanning 21 days.

Hematological profile of post-chemotherapy means the quantification result of hematological parameters after finishing the 4 cycles of chemotherapy treatments.

5.12 Ethical considerations

The Department of Medical Laboratory Science was provided ethical approval. To obtain approval for conducting the study, a support letter was written for WCSH. Oral informed consent was obtained from research participants by describing the purpose of the study, risks, benefits, confidentiality, and their right to refuse participation and withdraw at any time. During data collection, privacy was respected, and data confidentiality was ensured.

5.13 Dissemination of the result

The thesis will be presented at the Department of Medical Laboratory Sciences. The results will be communicated to the relevant stakeholders at various conferences, and the final results will be published in journals.

6 Result

6.1 Sociodemographic and Clinical Characteristics of Breast Cancer Patients Undergoing Chemotherapy at WCSH

In this study, a total of 43 female breast cancer patients receiving chemotherapy at the Worabe Comprehensive Specialized Hospital were included. As shown in Table 1 below, the median age of the study participants was 39 years, with an interquartile range of 34 to 50 years. Most of the participants (23, 53.5%) were within the age group of 31-45 years, followed by those aged 46-65 (11, 25.6%). Regarding their residence, 29 (67.4%) participants live in rural areas, 31 (72.1%) were married, and the majority (22, 51.2%) had a primary level of education.

Regarding WHO group staging, 4 (9.35%) of the study participants were in stage I, 14 (32.6%) in stage II, 13 (30.6%) in stage III, and 12 (27.9%) in stage IV at the time of chemotherapy initiation. Anatomically, 26 (60.5%) cancer initiation sites were left-sided, while the remaining 39.5% were right-sided. Metastasis frequencies were as follows: liver (11.6%), lung (11.6%), bone (4.7%), and lymph nodes (30.2%).

Table 1: Socio-demographic and clinical characteristics of breast cancer patients at WCSH, Worabe, central Ethiopia, from December 2023 to December 2024, N=43

Variable	Category	Number	Percent
Age (years)	≤ 30	6	14.0
	31-45	23	53.5
	46-65	11	25.6
	> 65	3	7.0
Residence	Urban	14	32.6
	Rural	29	67.4
Occupation	Employed	10	23.3
	Unemployed	20	46.5
	Farmer	13	30.2
Educational background	No formal education	13	30.2
	Primary education	22	51.2
	Secondary education and above	8	18.6
Marital status	Married	31	72.1
	Divorced	3	7.0
	Widowed	9	20.9

Stage of cancer	Stage I	4	9.3
	Stage II	14	32.6
	Stage III	13	30.2
	Stage IV	12	27.9
Anatomical site of the cancer	Left Breast	26	60.5
	Right Breast	17	39.5
Metastasis	Not metastasis	18	41.9
	Metastasis to Liver	5	11.6
	Metastasis to Lung	5	11.6
	Metastasis to Bone	2	4.7
	Metastasis to Lymph node	13	30.2
	Total	**43**	**100%**

6.2 The Effect of Chemotherapy on RBC Parameters in Breast Cancer Patients Attending WCSH

The results shown in Figures 1 and 2 indicate significant hematological parameter changes in breast cancer patients after undergoing chemotherapy. A significant decrease ($P < 0.05$) was observed in the median (IQR) values of RBC count, hemoglobin concentration, hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration after completion of four chemotherapy cycles compared to baseline. Specifically, the RBC count reduced from 4.70 (4.36–5.00) $\times 10^6$/µl to 4.27 (3.83–4.71) $\times 10^6$/µl, hemoglobin concentration decreased from 13.60 (12.8–14.9) g/dl to 12.60 (11.1–13.2) g/dl, HCT reduced from 39.6 (37.6–42.4)% to 36.7 (33.5–39.5)%, MCH decreased from 29.3 (28.6–30.5) pg to 28.9 (27.6–30.0) pg, and MCHC declined from 34.3 (33.2–35.0) g/dl to 33.3 (32.6–34.3) g/dl. But a significant increase ($P < 0.01$) in red cell distribution width was seen, from 42.2(40.2–47.3) % to 48.6(44.0–55.1) % after completion of the cycle.

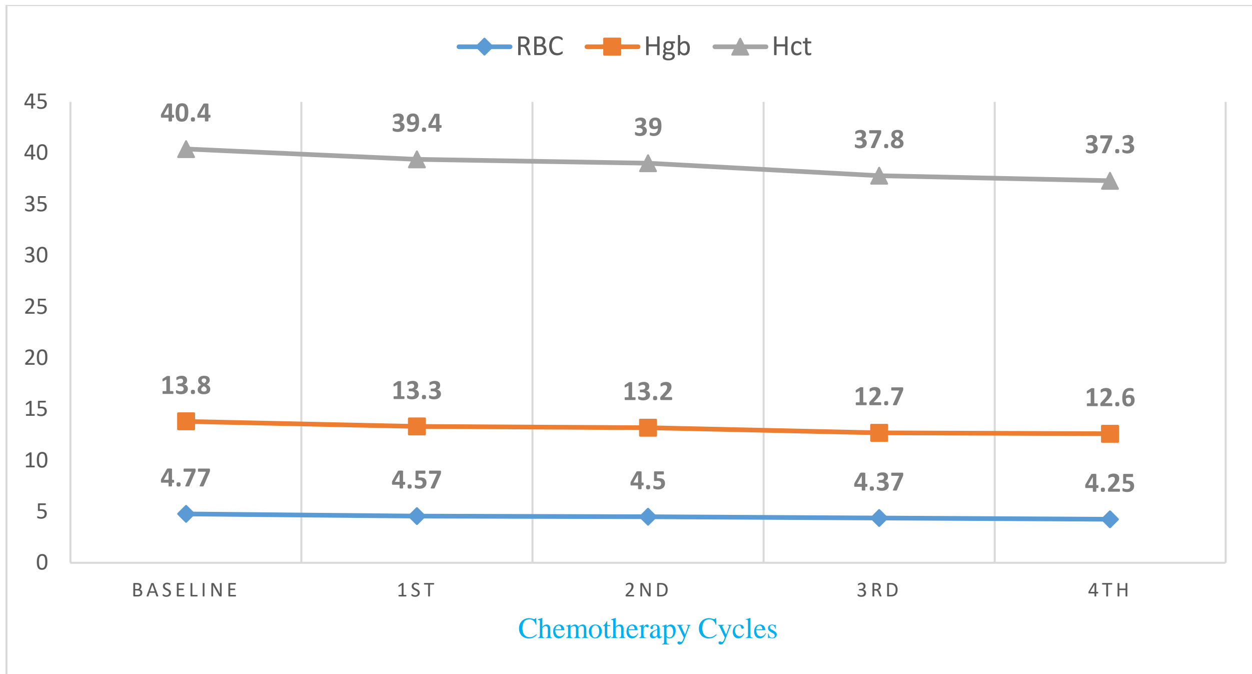

Figure 1: Change in red blood cell parameters (RBC count, Hemoglobin, and Hematocrit) in the different cycles of breast cancer chemotherapy at WCSH, Worabe, central Ethiopia

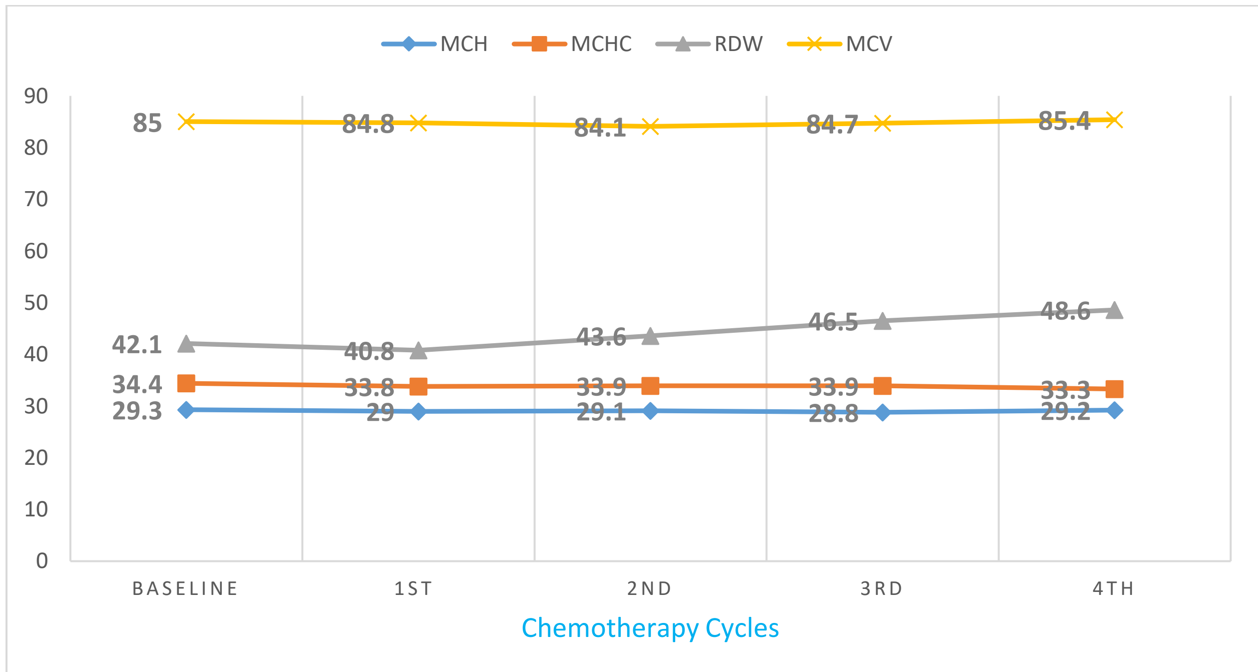

Figure 2: Change in red blood cell parameters (Mean Cell Volume, Mean Cell Hemoglobin, Mean Cell Hemoglobin Concentration, and Red Cell Width) in the different cycles of breast cancer chemotherapy at WCSH, Worabe, central Ethiopia

6.3 The Effect of Chemotherapy on WBC Parameters and Platelet Count in Breast Cancer Patients Attending WCSH

Most of the WBC parameters showed significant reductions ($P < 0.05$) in median (IQR), after completion of four cycles in compared with baseline counting, total WBC counts decreasing from 6.17 (4.75–7.99) $\times10^3/\mu l$ to 5.38 (4.29–6.96) $\times10^3/\mu l$, neutrophil counts declining from 3.37 (2.43–5.11) $\times10^3/\mu l$ to 2.90 (2.31–4.29) $\times10^3/\mu l$, and lymphocyte counts falling from 2.06 (1.53–2.70) $\times10^3/\mu l$ to 1.48 (1.24–1.90) $\times10^3/\mu l$, while monocytes, eosinophils, and basophils showed no significant change. The data is displayed in Figures 3 and 4.

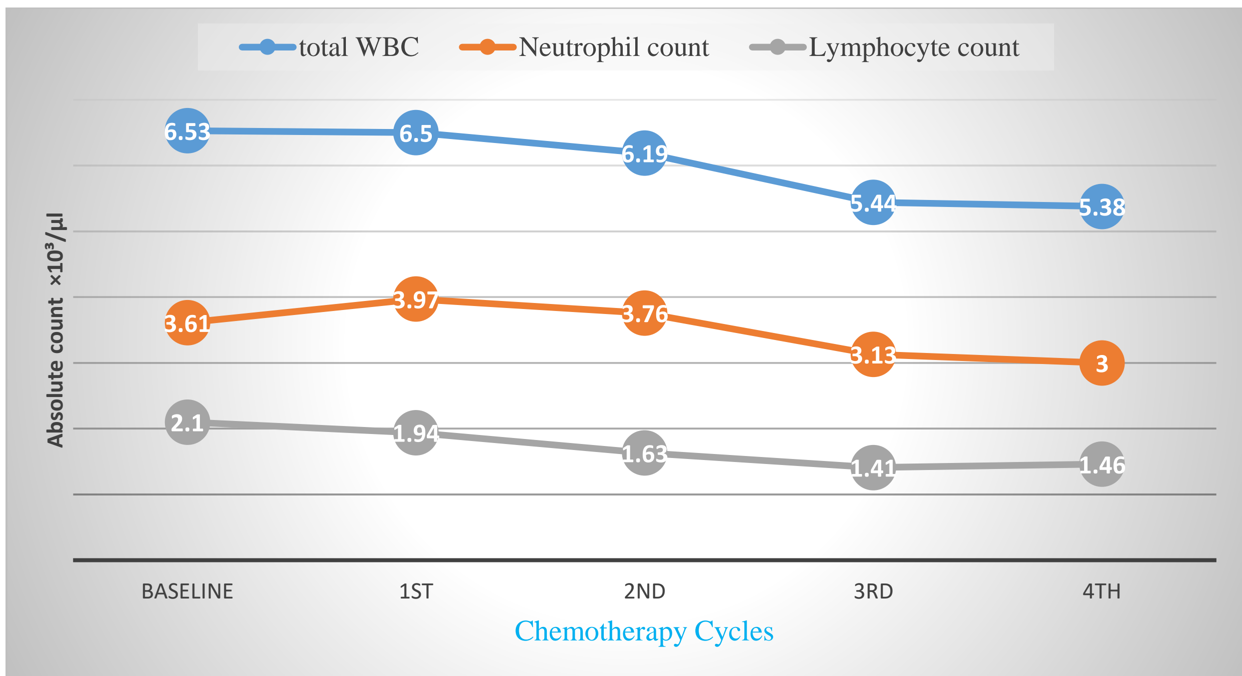

Figure 3 Variation in White blood cell parameters (total White Blood Cell, Neutrophil count, and Lymphocyte count) in the different cycles of breast cancer chemotherapy at WCSH, Worabe, central Ethiopia

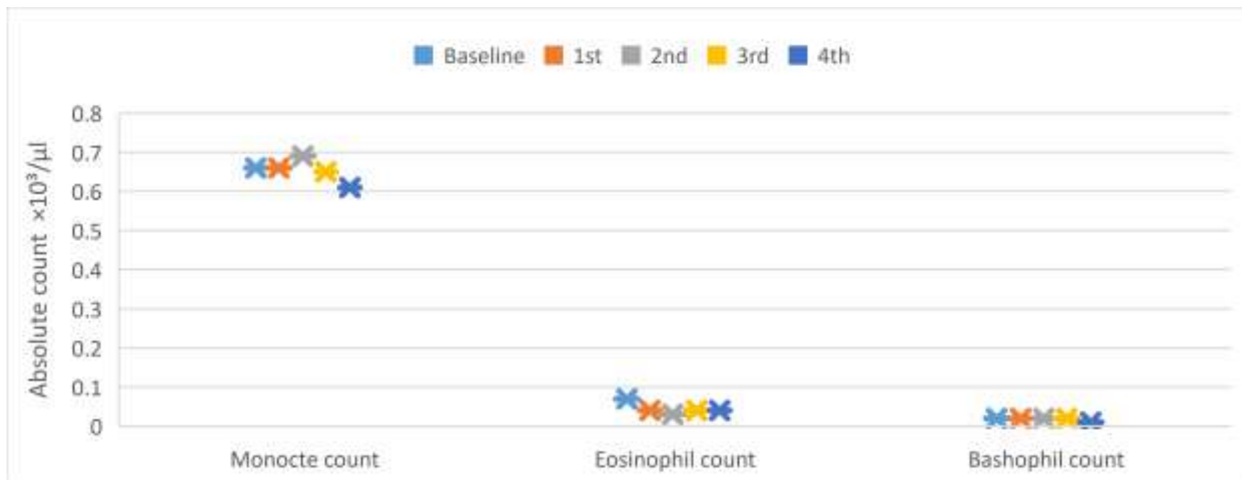

Figure 4: Variation in White blood cell parameters (Monocyte, Eosinophil, and Basophil count) in the different cycles of breast cancer chemotherapy at WCSH, Worabe, central Ethiopia

The platelet count increased from 293 (238–393) $\times 10^3/\mu l$ before chemotherapy initiation to 352 (273–434) $\times 10^3/\mu l$ after completing chemotherapy cycles, but this change was not statistically significant ($P > 0.05$) shown in Figure 5.

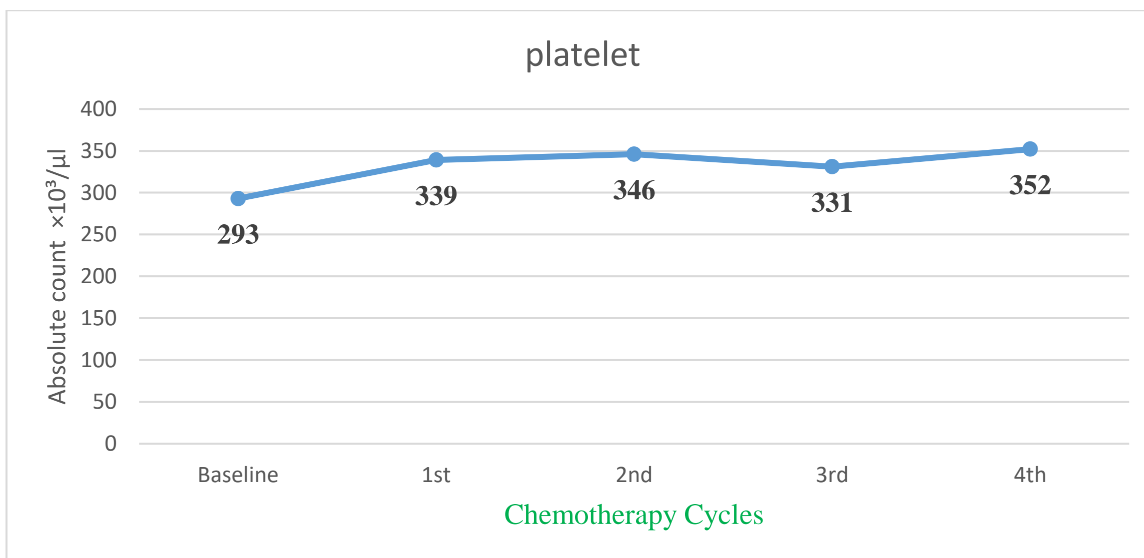

Figure 5: Variation in platelet count at different cycles of breast cancer chemotherapy in WCSH, Worabe, central Ethiopia

In general, most of the hematological parameters decline after completion of chemotherapy in contrast with baseline, but some parameters, like RDW, show an increment, and others, like mean cell volume and monocyte count, are not significantly changed.

6.4 The distributional differences of RBC parameters across the categories of socio-demographic and clinical factors

The results shown in Table 2 indicate that the distribution of RBC count showed significant variation (p=0.004) between stages of breast cancer at the baseline phase. This indicates the RBC count before initiation of chemotherapy varies based on the stage of cancer. However, after initiation of chemotherapy, no statistically significant variation in RBC distribution was observed across stages. As we have seen, the difference in pairwise comparisons of cancer stages to identify the difference is in which group, significant distribution is observed between Stage IV and Stage II (adjusted p = 0.049) and between Stage IV and Stage I (adjusted p = 0.006). but the other comparison did not show a statistically significant difference. The RBC distribution was significantly affected at baseline by residence (p=0.03) and anatomical site (p=0.05) during the second chemotherapy cycle, while other factors, including age, marital status, educational background, and metastasis to different parts of the body, had no significant effect across different cycles.

The hemoglobin levels show a significant variation across urban and rural patients after the first and second chemotherapy cycles (p=0.007, p=0.009, respectively). Clinical factors like anatomical site of the breast (p=0.024) and metastasis to internal part of the body (p=0.049) were significant after the second cycle, while stage of the stage of cancer (p=0.016) and metastasis to internal part of the body (p=0.016) became significant after the completion of 4th chemotherapy. Although in Kruskal-Wallis H test, significance p-values suggest potential differences in some comparisons, none of them are statistically significant differences after applying the Bonferroni correction post hoc test for multiple tests. Hematocrit significantly varied according to stage of cancer at baseline (p=0.049) and the end of the fourth cycle (p=0.013). Residence and metastasis both are significantly influence the hematocrit levels, with differences observed based on residence at the initial stage (p=0.008) and due to metastasis during the second cycle (p=0.014) and after the fourth cycle (p=0.018). After adjusting for multiple comparisons, there is only a significant difference in hematocrit levels seen between Stage IV and Stage I (p=0.043, Bonferroni-corrected), indicating that the majority of variations in hematocrit values across metastatic sites are not statistically significant.

In terms of mean cell volume, there were significant differences between cancer stages after the first cycle of chemotherapy (p=0.037), suggesting that red blood cell size varied according to stage. Educational background showed a distributional difference at the second and third cycles of chemotherapy. After pairwise correction with Bonferroni correction, the difference is shown between non-formal education and secondary education and above in both cycles. Age also had an impact on MCV, with significant differences after the third cycle of chemotherapy (p=0.042) and after completion of 4th cycle(p=0.049). While no significant variations in MCV were seen among different age groups, a significant difference in MCV was shown between Stage I and Stage IV cancers after applying the Bonferroni correction for multiple comparisons

Mean cell hemoglobin variation significantly occurs with the stage of cancer at baseline (p=0.020), suggesting changes in hemoglobin content during disease progression. Mean cell hemoglobin concentration was also significantly influenced by residence at baseline (p=0.022) and after the second chemotherapy cycle (p=0.010). Additionally, age-related differences in MCHC became significant after completion 4th cycle of chemotherapy (p=0.024). Red cell distribution width (RDW) varied significantly based on the anatomical site of the cancer at baseline (p=0.033) and after the first cycle of chemotherapy (p=0.011). RDW also differed significantly in relation to metastasis at baseline (p=0.033), highlighting the systemic impact of advanced disease. The Bonferroni correction showed no significant differences in metastasis types at adjusted p<0.05.

Table 2: Significance level of Kruskal-Wallis H and Mann-Whitney U Tests for Red Blood Cell Parameters by Sociodemographic, Clinical Variables, and Chemotherapy Phases in Breast Cancer Patients at WCSH, Worabe, Central Ethiopia (December 2023 - December 2024)

Hematological parameter		Socio-demographic and clinical factors							
		Age	**Residence**	**Marital status**	**Educational background**	**Occupation**	**Stage**	**Anatomical site**	**Metastasis**
RBC	**Baseline**	.857	.147	.413	.303	.966	.004	.664	.097
	1st	.226	.058	.359	.050	.361	.132	.308	.258
	2nd	.386	.003	.713	.128	.072	.059	.050	.091
	3rd	.335	.150	.780	.236	.589	.222	.164	.192
	Complete	.350	.064	.593	.259	.480	.056	.061	.108
HGB	**Baseline**	.969	.058	.349	.891	.931	.086	.479	.132
	1st	.209	.007	.516	.085	.126	.599	.237	.290
	2nd	.261	.009	.936	.250	.107	.139	.024	.049
	3rd	.118	.331	.519	.165	.836	.175	.126	.124
	Complete	.096	.119	.287	.791	.525	.016	.071	.016
HCT	**Baseline**	.988	.090	.435	.808	.752	.049	.243	.135
	1st	.115	.008	.397	.103	.137	.298	.184	.332
	2nd	.433	.041	.947	.429	.195	.120	.014	.067
	3rd	.091	.551	.381	.302	.974	.258	.084	.250
	Complete	.284	.049	.320	.676	.475	.013	.059	.018
MCV	**Baseline**	.562	.259	.196	.265	.775	.071	.559	.202
	1st	.642	.551	.141	.092	.756	.037	.487	.137
	2nd	.113	.190	.504	.032	.927	.148	.269	.130
	3rd	.042	.117	.054	.007	.865	.329	.628	.194
	Complete	.049	.186	.051	.066	.506	.337	.210	.208
MCH	**Baseline**	.625	.697	.829	.157	.906	.020	.941	.385
	1st	.261	.697	.421	.027	.871	.213	.980	.566
	2nd	.445	.311	.349	.547	.699	.199	.419	.277
	3rd	.559	.746	.466	.087	.772	.627	.990	.557
	Complete	.307	.603	.367	.340	.942	.486	.690	.201
MCHC	**Baseline**	.728	.022	.396	.392	.181	.448	.263	.117
	1st	.640	.856	.616	.611	.623	.134	.164	.130
	2nd	.102	.010	.512	.104	.299	.481	.681	.146
	3rd	.559	.123	.491	.116	.921	.717	.463	.482
	Complete	.024	.604	.293	.274	.969	.636	.551	.417
RDW	**Baseline**	.309	.254	.323	.263	.556	.093	.033	.033
	1st	.716	.294	.227	.522	.547	.381	.011	.199
	2nd	.507	.052	.252	.434	.142	.263	.093	.133
	3rd	.526	.001	.642	.112	.091	.803	.980	.161
	Complete	.943	.012	.634	.246	.088	.737	.576	.342

- The analysis carried out by Kruskal-Wallis H and Mann-Whitney U tests

6.5 The distributional differences of WBC parameters and Platelet count across the categories of socio-demographic and clinical factors

The findings summarized in Table 3, based on the Kruskal-Wallis H and Mann-Whitney U tests, demonstrate differences in white blood cell parameters and platelet counts associated with socio-demographic and clinical factors throughout various chemotherapy cycles. At baseline, no significant differences in total WBC counts were found across any of the studied factors. However, after the second cycle of chemotherapy, significant differences were seen related to residence ($p = 0.030$) and the stage of cancer ($p = 0.036$). At the end of the fourth cycle, a slightly significant difference was shown concerning the stage of cancer ($p = 0.048$). The analysis of total WBC counts across different cancer stages, adjusted with the Bonferroni correction, indicated a significant difference between Stage IV and Stage I ($p = 0.035$). No significant differences were found in the comparisons of other stages. This indicates that clinical factors, particularly the stage of cancer, may play a role in influencing total WBC counts as chemotherapy progresses.

At baseline, neutrophil counts showed significant differences linked to marital status ($p = 0.020$). In the second cycle, significant differences were noted for residence ($p = 0.023$) and cancer stage ($p = 0.044$). This pattern continued into the third cycle, where residence displayed highly significant differences ($p = 0.006$). A statistically significant difference in neutrophil counts was observed exclusively between Stage II and Stage I (Adj. Sig.=0.039) following Bonferroni correction, indicating a possible correlation between cancer stage and neutrophil levels at these stages.

The distribution of lymphocytes was showed significant differences in marital status during before starting chemotherapy ($p=0.007$), after the second cycle of chemotherapy ($p=0.050$), after the third cycle of chemotherapy ($p=0.016$), and after completion four cycle ($p=0.013$), while occupation showed significance before starting chemotherapy ($p=0.004$) and after the first cycle of chemotherapy ($p=0.006$). After implementing the Bonferroni correction, the analysis revealed no statistically significant differences in lymphocyte counts among marital status groups. However, a marked variation in lymphocyte counts was observed between individuals older than 65 and those aged 30 or less, suggesting that extreme age may influence lymphocyte distribution. And between farmers and employed people on occupation. Monocyte levels displayed significant differences for marital status ($p=0.028$) after the second cycle of chemotherapy. However, after applying the

Bonferroni correction to account for multiple comparisons, the variations in monocyte counts among different marital groups were no longer statistically significant. For eosinophils, occupation was significant after the first cycle of chemotherapy (p=0.018), and the anatomical site also showed significance after the first cycle of chemotherapy (p=0.003). Basophil count showed significant differences related to age before starting chemotherapy (p=0.045) and after the third cycle (p=0.052), residence after the fourth cycle (p=0.029), marital status after the third cycle (p=0.010), and the anatomical site after the fourth cycle (p=0.032). However, the multiple comparison analysis revealed no statistically significant differences in basophil counts among the various age categories.

In general, socio-demographic factors like marital status, occupation, and residence frequently showed significant impacts on hematological parameters, particularly lymphocytes and basophils. Clinical factors, including stage and anatomical site, also influenced total WBCs and eosinophils at specific stages.

Finally, metastasis showed a significant difference in platelet counts before starting chemotherapy (p=0.045), while other factors were not statistically significant. after the third cycle of chemotherapy, stage (p=0.043), anatomical site (p=0.013), occupation(P=0.041) and metastasis (p=0.016) exhibited significant differences. After the second cycle of chemotherapy, stage (p=0.026) and anatomical site (p=0.001) were significant, with metastasis approaching significance (p=0.058). after the third cycle of chemotherapy, the anatomical site remained significant (p=0.004). after completion of four cycles, anatomical site (p=0.002) showed significant differences. The Bonferroni-adjusted pairwise comparisons indicated a significant difference in platelet counts only between patients with Stage IV and Stage III cancer. This finding implies that variations in platelet counts may be due to disease advancement or the effects of treatment within these specific stages. No significant differences were detected among the other stages. In terms of metastatic sites, the only statistically significant difference identified after Bonferroni correction was between metastasis to bone and metastasis to lymph nodes, with all other comparisons yielding non-significant results.

Table 3: Association of white blood cell parameters and platelet counts with socio-demographic and clinical variables across chemotherapy phases in breast cancer patients at WCSH, Worabe, Central Ethiopia, from December 2023 to December 2024

Hematological parameter		Socio-demographic and clinical factors							
		Age	Residence	Marital status	Educational background	Occupation	Stage	Anatomical site	Metastasis
WBC	Baseline	.308	.595	.056	.697	.225	.399	.352	.370
	1st	.792	.173	.395	.595	.917	.207	.911	.528
	2nd	.875	.030	.098	.618	.805	.036	.766	.704
	3rd	.856	.090	.495	.314	.811	.146	.352	.275
	Complete	.439	.414	.377	.619	.426	.048	.434	.403
NEUT	Baseline	.325	.678	.020	.711	.325	.097	.568	.745
	1st	.661	.136	.398	.349	.763	.094	.297	.224
	2nd	.741	.023	.173	.477	.740	.044	.785	.585
	3rd	.589	.006	.359	.198	.545	.202	.371	.231
	Complete	.406	.243	.623	.569	.146	.090	.223	.196
LYMP	Baseline	.303	.350	.007	.760	.004	.565	.872	.070
	1st	.142	.815	.119	.245	.006	.812	.051	.792
	2nd	.100	.959	.050	.446	.369	.578	.471	.790
	3rd	.028	.213	.016	.286	.257	.312	.881	.571
	Complete	.052	.371	.013	.402	.227	.334	.526	.927
MONO	Baseline	.254	.856	.604	.224	.830	.480	.804	.251
	1st	.487	.969	.146	.739	.677	.716	.646	.481
	2nd	.929	.294	.028	.472	.116	.455	.180	.750
	3rd	.646	.969	.198	.333	.193	.152	.104	.217
	Complete	.307	.460	.055	.337	.166	.372	.747	.324
EOS	Baseline	.157	.603	.668	.124	.743	.125	.058	.069
	1st	.882	.773	.724	.616	.018	.577	.003	.209
	2nd	.713	.432	.925	.430	.354	.333	.120	.439
	3rd	.388	.567	.450	.412	.871	.380	.592	.116
	Complete	.265	.706	.282	.412	.957	.157	.144	.865
BAS	Baseline	.045	.491	.795	.149	.080	.483	.260	.353
	1st	.646	.281	.101	.926	.781	.136	.346	.198
	2nd	.240	.968	.698	.580	.866	.700	.346	.079
	3rd	.052	.489	.010	.402	.844	.689	.294	.538
	Complete	.146	.029	.101	.195	.571	.450	.032	.504
PLT	Baseline	.295	.276	.286	.990	.624	.069	.449	.045
	1st	.678	.659	.335	.662	.210	.043	.013	.016
	2nd	.156	.650	.112	.476	.469	.026	.001	.058
	3rd	.142	.846	.098	.500	.041	.250	.004	.425
	Complete	.185	.887	.163	.280	.059	.155	.002	.211

- The analysis carried out by Kruskal-Wallis H and Mann-Whitney U tests

7 Discussion

Chemotherapy is a fundamental treatment for breast cancer. It is a cytotoxic drug, primarily targets actively dividing cells. While effective against rapidly proliferating cancer cells, it also affects healthy cells with high multiplication, such as those in the bone marrow responsible for blood cell production. This collateral damage can lead to significant hematological abnormalities, including anemia and an increased risk of infection, which can cause serious health risks for breast cancer patients undergoing treatment(46, 56).

In this study, 53.5% of the study participants were within the age group of 31-45 years, a finding comparable with different studies conducted in Ethiopia (18-45 years (55.4%)) (27) but not with a study conducted in Nigeria 45-65(50.4%))(54), Congo(57), and Iraq(58). which could be attributed to differences in lifestyle, diet, genetic characteristics, population characteristics, and related factors.

The current study showed that a most of red blood cell parameters, such as RBC count, hematocrit, hemoglobin, mean cell hemoglobin and mean cell hemoglobin concentration were significantly decrease from the initiation to the completion of chemotherapy cycles, while, mean cell volume remains relatively stable, suggesting erythrocyte size is unaffected and Red Cell Distribution Width increases, reflecting greater variability in red blood cell size, which can result from the release of immature red blood cells into the circulation as a compensatory response to anemia. This indicates that the degree of anemia increased throughout treatment. Anemia is a common side effect of chemotherapy and can lead to symptoms such as fatigue and a decreased capacity for oxygen transport in the bloodstream(59).

This decline is primarily due to the myelosuppressive effects of chemotherapy agents, which impair the bone marrow's ability to produce new blood cells, leading to ineffective erythropoiesis. It may also be linked to oxidative stress from treatment that disrupts the production of red blood cells and damages mature ones. It is also by oxidation and blocking the addition of iron to the hemoglobin molecule that further complicates hemoglobin synthesis. Chemotherapy increases inflammatory cytokines, which reduce erythropoietin production and hinder erythropoiesis. A significant drop in red blood cell count after chemotherapy is likely due to higher pro-

inflammatory cytokines like IL-1, IL-6, TNF-α, and INF-γ that cause iron retention, impacting erythroid precursors(60, 61).

In parallel with this finding, the study conducted in Uttar Pradesh, India(53), Algeria(62), breast cancer patients receiving chemotherapy showed a significant decrease in RBC count, hemoglobin level, and hematocrit. Another study conducted in Tikur Anbesa comprehensive specialized hospital(22), Addis Ababa, and the University of Gondar comprehensive specialized hospital cancer treatment center(27), Ethiopia, shows a significant decrement of RBC count, hemoglobin, and hematocrit value.

In line with the current study, the mean cell volume does not significant difference in studies Tikur Anbesa comprehensive specialized hospital, Ethiopia, by Fikremariam(22). The RDW value is significantly elevated, similar to the studies conducted in Gondar and Addis Ababa, Ethiopia. (22, 27), and Brazil(63).

In this study, most of the WBC parameters, such as total WBC count, neutrophil count, and lymphocyte count, were significantly decreased from baseline to after completion of 4 cycles. The decrease in the white blood cell count may be associated with the effects of breast cancer therapies on the bone marrow. Concurrently, these medications can adversely affect healthy tissues, including immune cells such as lymphocytes, leading to reduced immunological efficacy and the probability of survival. These findings align with previous research conducted in Nigeria (54), as well as in Gondar(27) and Addis Ababa(22), Ethiopia, which are similarly reported reductions in WBC parameters throughout treatment. Such consistent observations across different geographical locations highlight the prevalent impact of chemotherapy on immune cell dynamics and reinforce the need for ongoing research to better understand the implications of these changes for patient management and outcomes(64)

Analysis of monocyte, eosinophil, and basophil counts revealed no statistically significant changes across the different stages of chemotherapy (p-values of 0.383, 0.375, and 0.615, respectively). While slight fluctuations in median values were observed for monocytes throughout treatment and a minor initial decline was noted for eosinophils, these changes did not reach statistical significance. Basophil levels remained relatively stable with minimal variation. The findings of the current study regarding eosinophil counts diverge from those of a study conducted at Tikur Anbesa Specialized Hospital(22), where a significant increase in eosinophil count was observed

after completion of chemotherapy compared to baseline. This increase may be attributed to the inflammatory effects of chemotherapy, as rapidly developing drug-related eosinophilia is often associated with allergic reactions, aggressive inflammation, or malignancy(65). Similar to this study, no significant differences were observed in basophil and monocyte counts.

Platelet counts were found to be significantly increased among breast cancer patients undergoing chemotherapy. This finding aligns with other studies conducted in Uttar Pradesh, India(53), and in Mekelle(24) and Addis Ababa(22), Ethiopia, which also reported an increase in platelet counts after completion of chemotherapy cycles. An earlier study suggested that this increase in platelet count could be attributed to reactive thrombocytosis, a condition that can arise as a consequence of chemotherapy-induced anemia. However, elevated platelet counts can also indicate enhanced platelet activity, organ inflammation, and even contribute to anxiety and depression-like symptoms. This suggests that breast cancer chemotherapy may exacerbate organ inflammation and contribute to anxiety disorders. Furthermore, systemic inflammation triggers the release of pro-inflammatory mediators such as interleukin-1 (IL-1), IL-3, and IL-6. These cytokines stimulate megakaryocyte proliferation, the cells responsible for platelet production within the bone marrow. When cells are damaged by anticancer drugs, they release chemicals that activate the immune system. This inflammatory response further stimulates platelet production(66, 67, 68)

In general, chemotherapy for breast cancer significantly impacts hematological parameters. This study found a significant decrease in red blood cell counts, hemoglobin, and hematocrit, consistent with findings from other studies. These changes are likely due to myelosuppression, oxidative stress, and increased inflammation. White blood cell counts, particularly neutrophils and lymphocytes, also decreased. Conversely, platelet counts were significantly elevated, potentially due to reactive thrombocytosis, inflammation, and the release of pro-inflammatory cytokines. While some parameters like monocytes, eosinophils, and basophils remained relatively stable, these findings highlight the multifaceted impact of chemotherapy on the hematopoietic system.

This study examined the impact of breast cancer stage on various red blood cell parameters, finding significant differences in RBC counts before starting chemotherapy, with Stage IV having the lowest counts. Although these differences reduced after treatment began, significant differences remained between Stage IV and Stages I and II. This supports a Spanish study showing the impact of cancer stage and metastasis on RBC counts(69). Consistent with the study conducted in Tigray,

Ethiopia(70), hemoglobin levels were lower in rural patients than in urban ones before chemotherapy. This difference was further influenced by the anatomical site of cancer and the presence of systemic metastasis. Hematocrit levels were also affected by cancer stage, residence, and metastasis, while other RBC parameters like MCV, MCH, MCHC, and RDW were influenced by cancer stage, age, residence, educational background, and metastasis at various treatment stages(69, 71)

Residence influences RBC parameters due to various interrelated factors, such as environmental influences and nutrition, which vary between urban and rural areas. The anatomical site of cancer also affects RBC parameters, as differences in tumor biology and disease progression can lead to varying hematological outcomes. In advanced cancer stages, increased tumor burden may cause anemia due to chronic inflammation, blood loss, and impaired bone marrow function. Advanced age may face more severe effects due to existing health issues and increased sensitivity to chemotherapy. Additionally, Metastasis can adversely impact RBC parameters by increasing the tumor burden, thereby affecting organs involved in RBC production, such as the bone marrow, and potentially compromising their function(72, 73)

This study investigated the impact of different sociodemographic and clinical factors on WBC parameters. Residence and cancer stage significantly affect total white blood cell count, with a marked disparity observed in white blood cell counts between patients with Stage IV and Stage I cancer. However, a study conducted in Nigeria found no statistically significant difference in WBC count across cancer stages(74). Neutrophil counts were influenced by marital status at the outset and by residence and cancer stage in subsequent treatment phases. Lymphocyte counts were significantly impacted by marital status throughout the treatment period, by occupation before and after the second cycle, and by patient age. Monocyte counts initially showed variations related to marital status and occupation after the second cycle of chemotherapy, but these differences were not statistically significant after adjustments. Eosinophil levels were significantly associated with occupation and the anatomical location of the cancer after the first cycle. Basophil counts were affected by age, residence, marital status, and the anatomical location of the cancer at various stages of treatment, although these differences were not statistically significant after adjustments. In conclusion, both sociodemographic factors such as marital status, occupation, residence and clinical factors stage of cancer, metastasis and anatomical site of the cancer significantly impact

hematological parameters during chemotherapy cycles, while most other studies conducted in different regions have not proved a significant effect of these sociodemographic factors(75, 76).

Variations in platelet counts during chemotherapy are significantly affected by the stage of cancer, particularly between Stage IV and Stage III, and the anatomical site of the breast. While the age of the patient initially affected platelet count before initiation of chemotherapy, the stage of cancer and anatomical site of the breast remained significant factors of platelet count variations throughout chemotherapy cycles, especially after the second and third cycles of chemotherapy. In contrast to the current study, studies conducted in Makassar, Indonesia(77), and China(78) did not find a statistically significant relationship between increased platelet count and cancer stage.

8 Strengths and Limitations of the Study

8.1 Strength

- Data were collected over five time points
- In Ethiopia, there is no published research; the data were collected at each cycle, so the study serves as the baseline for other researchers
- The data collected was a primary source, minimizing potential bias

8.2 Limitation

- The sample size for this study was relatively small
- Due to the non-normal distribution of the data, rank-based tests were used for analysis
- Many articles lack analysis of certain parameters, such as MCH, MCHC, eosinophil count, and basophil count, challenging for comparison with other studies.

9 Conclusion and Recommendation

9.1 Conclusion

This study observed significant decreases in several red blood cell parameters, including RBC count, hemoglobin, and hematocrit after completion 4th cycle. WBC parameters, particularly total WBC, neutrophils, and lymphocytes, also declined. In contrast, red cell distribution width increased, while platelet counts showed a non-significant increase. These findings highlight the substantial impact of chemotherapy on various hematological parameters. This study explored how various factors affect hematological parameters in breast cancer patients receiving chemotherapy. Key findings revealed significant variations in RBC counts across different cancer stages. Hemoglobin levels were influenced by residence, while hematocrit levels were affected stage of cancer. Other factors like age, stage of cancer, and the anatomical site of the breast also significantly affected most of the parameters

9.2 Recommendation

- Patients on chemotherapy should be closely monitored for their hematological profile
- Further research is recommended with a large sample size to investigate the impact of associated factors, such as lifestyle and nutritional status, on the reduction of hematological parameters.
- Further research is recommended to investigate long-term (eight-cycle) effects of chemotherapy on hematological parameters

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Annex - I

Participant information sheet (English version)

You have been chosen as a participant in this study, which is an assessment of hematological parameters alteration and associated risk factors among breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital, Worabe, central Ethiopia. Please read the following statement and ask any unclear questions before you agree to participate.

The objective of this study is to assess hematological parameters alteration and associated risk factors among breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital from December 2023, to December 2024, Worabe, central Ethiopia. This information sheet is prepared by the principal investigator, Abdilaziz Nassir, to clarify the study which you are asked to take part. If there is any lack of clarity, you decide to participate or not, you can ask freely.

You will be requested to give a 3-4 ml blood sample collected from your arm using sterile tubes. If you agree to give a blood sample, then you will also be asked to answer for questionnaire.

Any information that we collect about you during this study will be kept confidential. Your personal information will be stored securely following the documentation of your file and will be maintained in a protected location. Only the principal investigator will be able to link your identity with the code number.

There is no direct benefit you obtain from this study, but indirectly, the result of the study will be beneficial to put a new strategy for the assessment of hematological parameters alteration and associated risk factors among breast cancer patients receiving chemotherapy at Worabe Comprehensive Specialized Hospital, Worabe, central Ethiopia. Hence, you are indirectly benefiting other breast cancer patients and society in this respect. There is no risk of gain during the study, except that you may feel a mild pain during sample collection. We are asking you and others to voluntarily participate in this study. Participation in this study is entirely voluntary. You can refuse to participate in this research at any time, and your refusal to participate in this study will not affect any of the benefits you are supposed to get from the hospital. Please contact any questions or problems you may encounter during this study to the principal investigator.

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Annex - II

Participant information sheet (Amharic version)

በዚህ ጥናት ውስጥ (assessment of hematological parameters alteration and associated risk factors among receiving chemotherapy breast cancer patients at Worabe comprehensive specialized hospital, Worabe, central Ethiopia) ተሳታፊ እንዲሆኑ ተመርጠዋል። ለመሳተፍ ከመስማማትዎ በፊት እባክዎ የሚከተለውን መግለጫ ያንብቡ እና ማንኛውንም ግልጽ ያልሆነ ጥያቄ ካለ ይጠይቁ።

የዚህ ጥናት ዓላማ ከታህሳስ 2023 እስከ ታህሳስ 2024 በወራቤ አጠቃላይ ስፔሻላይዝድ ሆስፒታል ኬሞቴራፒ የሚወስዱ የጡት ካንሰር ታማሚዎች ላይ የሄማቶሎጂ መለኪያዎችን እና ተያያዥ አደጋዎችን ለመገምገም ነው። እርስዎ እንዲሳተፉ የተጠየቁበትን ጥናት ለማብራራት ይህ የመረጃ ወረቀት የተዘጋጀው በዋናው መርማሪ አብድአዚዝ ናስር ነው። ግልጽነት የጎደለው ነገር ካለወይም ለመሳተፍ ከወሰኑ በነጻነት መጠየቅ ይችላሉ።

ንጽህናው በተጠበቀ የናሙና መሰብሰቢያ ቱቦ በመጠቀም ከእጅዎ ላይ 3-4 ሚሊሊትር የደም ናሙና እንዲሰጡ ይጠየቃሉ። የደም ናሙና ለመስጠት ከተስማሙ ለመጠይቁ መልስ እንዲሰጡ ይጠየቃሉ። በዚህ ጥናት ወቅት ስለእርስዎ የምንሰበስበው ማንኛውም መረጃ በሚስጥር ይጠበቃል። ስለ ማንነትዎ መረጃ ፋይልዎን ከተቀዳ በኋላ ይቀመጣል; እና ደህንነቱ በተጠበቀ መልኩ ይያዛል። ማንነትዎን ከኮድ ቁጥሩ ጋር ማገናኘት የሚችለው ዋናው መርማሪ ብቻ ነው።

ከዚህ ጥናት የምታገኙት ቀጥተኛ ጥቅም የለም ነገር ግን በተዘዋዋሪ የጥናቱ ውጤት በወራቤ አጠቃላይ ስፔሻላይዝድ ሆስፒታል ወራቤ ኮምፐረሄንሲቭ ስፔሻላይዝድ ሆስፒታል ኬሞቴራፒ የሚወስዱ የጡት ካንሰር ታማሚዎች ላይ የሄማቶሎጂ መለኪያዎችን እና ተያያዥ አደጋዎችን ለመገምገም እና አዲስ ስልት ማስቀመጥ ጠቃሚ ይሆናል።

ስለዚህ በተዘዋዋሪ ሌሎች የጡት ካንሰር ታማሚዎችን እና ማህበረሰቡን በዚህ ረገድ እየጠቀማችሁ ነው። በጥናቱ ወቅት ናሙናዎች በሚሰበሰቡበት ጊዜ መጠነኛ ህመም ሊሰማዎት ከመቻሉ በስተቀር ምንም አይነት የአደጋ ስጋት የለም። እርስዎ እና ሌሎች በዚህ ጥናት ውስጥ በፈቃደኝነት እንዲሳተፉ እንጠይቃለን። በዚህ ጥናት ውስጥ መሳተፍ ሙሉ በሙሉ በፈቃደኝነት ነው። በዚህ ጥናት ውስጥ በማንኛውም ጊዜ ለመሳተፍ እምቢ ማለት ይችላሉ እና በዚህ ጥናት ላይ ለመሳተፍ ፈቃደኛ አለመሆንዎ ከሆስፒታል ማግኘት ያለብዎትን ማንኛውንም ጥቅም አያስቀርም። እባክዎ በዚህ ጥናት ወቅት ሊያጋጥሙዎት የሚችሉትን ማንኛውንም ጥያቄዎች ወይም ችግሮች ለዋናው መርማሪ ያነጋግሩ።

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Annex -III

Consent format

MRN No.__________

I have read the provided information (or it has been read to me), I have been allowed to ask questions, which have been answered to my satisfaction, and I voluntarily consent to participate in this study

I consent to the collection of my blood for this study and am aware that I have the option to withdraw from the study at any time.

Print the name of the participant, date, and the signature or thumb impression of the participant

____ ____ /____ /____ (dd-mm-yy) ___________

If illiterate;

Print name of independent literate witness, date, and signature of witness (if possible, this person should be selected by the participant and should have no connection to the research team)

____ ____ /____ /____ (dd-mm-yy) ___________

Phone number ________________________________

Print name of researcher, date and signature of researcher

____ ____ /____ /____ (dd-mm-yy) ___________

Annex - IV

English version of the data gathering tool (Questionnaire and checklist)

Part I: Socio-demographic characteristics		
S.no	**Variable**	**Response**
1.	Sex	1. Male 2. Female
2.	Age	__________ (years)
3.	Marital status	1. Single 2. Married 3. Divorced 4. Widowed
4.	Educational background	1. No formal education 2. Primary education (1-8) 3. Secondary education (9-12) 4. Higher education
5.	Residence	1. Urban 2. Rural
6.	Occupation	1. Government employee 2. Non-government employee 3. Farmer 4. Self-employed 5. Housewife 6. Retired 7. Unemployed 8. Others (specify)

Part II: Clinical Characteristics		
1.	Stage of the cancer	1. Stage I 2. Stage II 3. Stage III 4. Stage IV
2.	Anatomical site of the cancer	1. Left Breast 2. Right Breast 3. Both
3.	Metastasis	1. Metastasis to the Liver 2. Metastasis to the Lung 3. Metastasis to Bone 4. Metastasis to the Lymph node 5. Other part of body, specify ______________ 6. No metastasis

Annex - V

Amharic version of the data collection Questionnaire

ክፍል አንድ፡ ማህበራዊ የስነህዝብ አወቃቀር ሁኔታን የሚያሳይ መጠይቅ		
1.	ፆታ	1. ወንድ 2. ሴት
2.	ዕድሜ	_______________ አመት
3.	የጋብቻ ሁኔታ	1. ያላገባ/ች 2. ያገባ/ች 3. የተፋቱ 4. የሞተችበት/ባት
4.	የትምህርት ደረጃ	1. መደበኛ ትምህርት ያልተከታተለ/ች 2. አንደኛ ደረጃ የተማረ/ች(1-8) 3. ሁለተኛ ደረጃ የተማረ/ች(9-12) 4. ከፍተኛ ትምህርት የተከታተለ/ች
5.	የመኖሪያ ቦታ	1. ከተማ 2. ገጠር
6.	ስራ	1. የመንግሰት ሰራተኛ 2. የመንግሰት ሰራተኛ ያልሆነ/ች 3. ገበሬ 4. ራስ አስተዳዳሪ 5. የቤት እመቤት 6. ጡረታ የወጣ/ች 7. ስራ የሌለው/ላት 8. ሌላ ከሆነ ይግለጹ------------

ክፍል ሁለት: ክሊኒካዊ ባህሪያት		
1.	የካንሰር ደረጃ	1. ደረጃ I 2. ደረጃ II 3. ደረጃ III 4. ደረጃ IV
2.	የካንሰር ያለበት የሰውነት ኣካል	1. የግራ ጡት 2. የቀኝ ጡት 3. ሁለቱም
3.	የካንሰር ስርጭት	1. ወደ ጉበት የተሰራጨ 2. ወደ ሳንባ የተሰራጨ 3. ወደ አጥንት የተሰራጨ 4. ወደ ሊምፍ ኖድ የተሰራጨ 5. ወደ ሌላ የአካል ክፍል፣ ይግለጹ_______________ 6. አልተሰራጨም

Annex - VI

Patient's Laboratory Hematological Profile Data Collection Form

MRN no ______________________

	Hematological parameters	**Before starting Chemotherapy treatment**	**After 1st cycle of chemo**	**After the 2nd cycle of chemo**	**After the 3rd cycle of chemo**	**After completion of the 4-cycle chemo**
1.	RBC ($10^6/\mu l$)					
2.	HGB (g/dl)					
3.	HCT (%)					
4.	MCV (fl)					
5.	MCH (pg)					
6.	MCHC (g/dl)					
7.	RDW (%)					
8.	WBC ($10^3/\mu l$)					
9.	NEU					
10.	LYMP					
11.	MON					
12.	EOS					
13.	BAS					
14.	PLT ($10^3/\mu l$)					

Annex VII

Declaration

The undersigned declares that this thesis complies with the regulations of the University and meets the accepted standards with respect to originality and quality. I also agree to accept responsibility for the scientific, ethical, and technical conduct of the research project and for the provision of required progress reports.

M.Sc. candidate: Abdilaziz Nassir (B.Sc.)

Signature: ___________________

Date of submission: ___________________

This thesis has been submitted with the approval of our advisors

Advisor: Fekadu Urgessa (MSc, PhD Candidate)

Signature: _____________________

Date: _____________________

Place: Addis Ababa, Ethiopia.

Advisor: Dr. Zemenu Tamir (MSc, PhD)

Signature: ____________________

Date: ____________________

Place: Addis Ababa, Ethiopia.