INVESTIGATING THE CORRELATION BETWEEN DEMOGRAPHIC AND COMORBIDITY PROFILES WITH CHEMOTHERAPEUTIC TOXICITY EXPERIENCES IN EARLY-STAGE BREAST CANCER PATIENTS IN A PRIVATE MEDICAL ONCOLOGY PRACTICE IN SOUTH AFRICA.

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Declaration

I, Chantelle Pienaar Minns, declare that this research report is my own, unaided work and has not been submitted before for any degree or examination at any other University. I have appropriately indicated and acknowledged all sources I used or quoted through complete references. This research report is being submitted for the Master of Science in Medicine Degree at the University of the Witwatersrand, Johannesburg.

C Minns

Chantelle Pienaar Minns

04 day of June 20 24 in Johannesburg

Dedication

I dedicate this study to my parents, James and Mary-Ann Minns. I appreciate all your sacrifices and the privileges I have access to because of you.

Abstract

Background: An estimated 24 million people will be diagnosed with cancer globally by 2050, with approximately 16.8 million expected to be residing in low- and middle-income countries. Breast cancer is one of the most prevalent types of cancer diagnosed in women worldwide and 23% of all diagnosed malignancies are attributed to breast cancer. The prevalence of chemotherapy-induced adverse drug reactions ranges globally between a vast 60 - 80% amongst patients, negatively impacting overall treatment outcomes.

Aim of study: This study aimed to determine a potential correlation between demographic profiles and the presence of pre-existing comorbidities on the chemotherapy-related adverse effects experienced by patients with stage 0-III breast cancer at a private oncology centre in Gauteng. Furthermore, interventions applied by the oncologists to mitigate the adverse effects were investigated and reported adverse events were compared to the WHO VigiAccess Adverse Drug Reaction database.

Methods: A quantitative, retrospective cohort analysis of patient charts from January 2018 to December 2019 at the private Sandton Oncology Centre was undertaken. The study sample size was 54 participants. Patient files were randomly selected. Demographic and comorbidity profiles, as well as the staging (0 – III) data were retrieved from patient medical charts, in accordance with the study inclusion criteria. Furthermore, the chemotherapeutic toxicities, experienced by patients, treated with a particular chemotherapeutic agent were reviewed. Interventions employed to alleviate toxicity were further recorded for data analysis (dose modifications, dose reductions, and premature discontinuation of oncology treatment). Descriptive statistics was analysed using pivot tables in Microsoft Excel. Inferential statistics was analysed with Stata software version 18. Ethical clearance was obtained before patient files were accessed and confidentiality of patient information was maintained throughout the study.

Results: Most patients included in the study were white (57.4%), aged 50 – 59 years (29.6%), and diagnosed with stage II breast cancer (48.2%). Most of the patients had tumours which were oestrogen (66.7%) and progesterone positive (57.4%) and Human Epidermal Growth Factor Receptor 2 (HER2) negative (48.2%). The majority of patients, irrespective of ethnicity, received a combination of an anthracycline and cyclophosphamide followed by a taxane (51.8%). The most documented comorbidities were hypertension, obesity, dyslipidaemia, and diabetes. Of those patients reporting adverse effects, 77.8% reported adverse effects after the

first cycle of chemotherapy. The chemotherapy-related adverse effects show similarity to the adverse effects reported on the World Health Organisation's VigiAccess Adverse Drug Reaction database, particularly adverse effects of the digestive, integumentary, haematological and lymphatic systems.

Conclusions: The number of comorbidities present increases with age. White patients with more comorbidities experienced more chemotherapy-related adverse effects. The majority of the patients for which dose reductions were implemented, experienced five or more adverse effects during their treatment. More than half of the termination of treatment cases were preceded by a dose reduction. No statistically significant correlation was found between any of the ethnic groups or age categories and the total number of adverse effects experienced. A statistically significant correlation was found between other comorbidities and the number of psychiatric adverse effects ($p=0.014$). Reported infections were significantly higher in patients with hypertension ($p=0.043$) and lymphatic system adverse effects were higher in patients with dyslipidaemia ($p=0.017$).

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List of abbreviations

5-FU – 5-Fluorouracil

ART – Antiretroviral Therapy

ABW – Actual body weight

AC – Adriamycin (Doxorubicin) and Cyclophosphamide

ADR – Adverse Drug Reaction

ADRs – Adverse Drug Reactions

BMI – Body Mass Index

BSA – Body Surface Area

BRCA – Breast Cancer Gene

CINV – Chemotherapy-induced nausea and vomiting

CIPN – Chemotherapy-induced peripheral neuropathy

CMF – Cyclophosphamide, Methotrexate and 5-Fluorouracil

CTCAE – Common Terminology Criteria for Adverse Events

CVD – Cardiovascular disease

CYP – Cytochrome

EC – Epirubicin and Cyclophosphamide

G-CSF – Granulocyte colony-stimulating factor

HDL – High-density lipoprotein

HER2 – Human Epidermal Growth Factor Receptor 2

HIV – Human Immunodeficiency Virus

HREC – Human Research Ethics Committee

LDL – Low-density lipoprotein

LVF – Left Ventricular Function

MDS – Myelodysplastic Syndrome

NSABP – National Surgical Adjuvant Breast and Bowel Project

PIDM – Programme for International Drug Monitoring

POPIA – Protection of Personal Information Act

SA – South Africa

SABCHO – South African Breach Cancer and HIV Outcomes

SEER – Surveillance, Epidemiology and End Results

TCH – Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab)

TNBC – Triple Negative Breast Cancer

VTE – Venous thromboembolism

WHO – World Health Organisation

Chapter 1: Introduction

1. Chapter overview

This chapter provides a background on cancer with specific reference to breast cancer. It provides insight into the short-and long-term adverse drug reactions that can be expected following treatment with a chemotherapeutic agent. This chapter also discusses the effect of age, ethnicity, HIV infection, diabetes, obesity, hypertension, and dyslipidaemia on the severity of adverse drug reactions experienced from oncology therapy use.

1.1 Background

Cancer is the foremost contributor to mortality in numerous wealthy nations (Whiteman and Wilson, 2016). In 2020, 19.3 million people were diagnosed with cancer, resulting in around 10 million deaths from various types of the disease. Of these, 683,100 women succumbed specifically to breast cancer (Sung *et al*., 2021). Approximately 24 million people are estimated to be diagnosed with cancer by 2050, with 16.8 million of those residing in economically developing countries (Kingham *et al.,* 2013).

Cancer care is fast becoming essential in sub-Saharan African countries. Lifestyle changes and advancements in modern medicine are attributed to the rise in cancer occurrences among certain population groups (Kingham *et al*., 2013). Unlike other regions, Africa has a higher proportion of cancer deaths (7.2%) compared to its share of cancer cases (5.7%) (Sung *et al*., 2021). Poor infrastructure, scarcity of healthcare workers, advanced stage of cancer at diagnosis, use of traditional therapies, limited treatment options, and poor treatment compliance all contribute to the high mortality rate among people living with cancer in emerging economic regions (Kingham *et al*., 2013).

In 2020, South Africa saw 108,168 new cancer cases (The Global Cancer Observatory, 2021), with a projected 112,921 new cases anticipated for 2023 (Singh *et al.,* 2015). According to statistics from the Global Cancer Observatory (2021), the prevalent cancer types diagnosed in women in South Africa in 2020 included breast, cervical, colorectal, lung, and endometrial cancers. In men, cancer of the prostate, lung and colorectum were most prevalent, along with Kaposi sarcoma and non-Hodgkin lymphoma (The Global Cancer Observatory, 2021). The most frequently diagnosed malignancy in women globally, requiring chemotherapeutic treatments, is breast cancer. Furthermore, the Cancer Association of South Africa (CANSA)

reported that South Africa might possess the highest incidence of male breast cancer cases worldwide (Herbst, 2021).

Approximately 1-3% of individuals diagnosed with breast cancer in South Africa are male (Herbst, 2021). With 23% of all malignancies presenting as breast cancer and 14% of overall cancer deaths attributable to breast cancer, a significant public health threat is posed, warranting research efforts to reduce breast cancer fatalities (Singh *et al.,* 2014).

1.2 Breast cancer staging and risk factors

A tumour in the breast develops when normal cells mutate and spread rapidly. In non-metastatic breast cancer (stage 0), the tumour is only present in the milk lobules (Ghai *et al*., 2021). Stage I breast cancer is a small primary invasive tumour without the involvement of lymph nodes. Regional lymph nodes are involved with stage II breast cancer. A large tumour fixed to the chest wall and extensive lymph node involvement characterises Stage III breast cancer (Wells *et al*., 2015). These tumour cells can infiltrate the surrounding organs or other body parts, known as metastatic cancer (stage IV). The surrounding tissue is infiltrated in approximately 80% of breast cancer cases (Ghai *et al*., 2021).

Risk factors predominantly linked to breast cancer are advancing age and gender, with additional variables including early onset of menstruation, absence of childbirth, delayed age at first birth, hormone replacement therapy, personal and family medical history, mutations in Breast Cancer Gene (BRCA) 1 and BRCA2 genes, as well as environmental and lifestyle factors, such as radiation exposure (Wells *et al*., 2015). Afifi *et al*. (2020) conducted a study in the United States and found that cardiovascular and cerebrovascular disease were among the most common non-breast cancer causes of death. Other significant non-cancer causes of death included chronic liver disease, septicaemia, various infectious and parasitic diseases, and suicide.

1.3 Treatment of breast cancer

Orthodox therapies for breast cancer are surgery, radiation, and chemotherapy (On *et al*., 2022). Patients diagnosed with early breast cancer usually undergo surgery and receive adjuvant systemic therapies to decrease the risk of local and metastatic disease recurrence (Hopwood *et al*., 2006). Chemotherapy, targeted therapy or hormone therapy are the systemic therapy options for managing breast cancer. Physicians should base the selection of systemic

therapy on the biological characteristics of the tumour, such as hormone and HER2 (human epidermal growth factor receptor 2) receptor status, proliferation, and grade, the tumour's stage, and the patient's comorbidities and preferences (Suter and Pagani, 2018).

Treatment of non-metastatic breast cancer regularly involves anthracycline-based treatment plans. The combination of chemotherapy and a dose-dense regimen proves more efficacious in breast cancer treatment than traditional treatment plans but results in higher levels of toxicity. According to the National Cancer Institute (2023), dose-dense chemotherapy treatment plans involve less time between cycles than conventional treatment plans (Han *et al*., 2011).

Some new advancements in breast cancer treatment include immunotherapy, hormone-based therapy, and stem cell therapy (Ghai *et al*., 2021). Ongoing efforts to address the high rates of relapse and disease progression in breast cancer have led to the development of new targeted therapies. These targeted therapies include HER2 inhibitors, phosphoinositide-3-kinase, v-akt murine thymoma viral oncogene homolog, mammalian target of rapamycin (mTOR) inhibitors, poly (ADP-ribose) polymerase inhibitors, cyclin-dependent kinase 4/6 inhibitors, vascular endothelial growth factor inhibitors, and immune checkpoint inhibitors (Ju *et al*., 2018).

1.4 Chemotherapeutic toxicity

1.4.1 Side effects versus adverse effects

The Centre for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) define a side effect as an adverse drug reaction. Their definition does not include positive or neutral side effects. The WHO defines a side effect as any unintended effect which occurs at a normal dose related to pharmacological properties (Due, 2023). The WHO's definition implies that side effects, although not the primary therapeutic aim, may be advantageous rather than harmful (Edwards & Aronson, 2000).

Adverse effects are any unwanted outcomes resulting from the use of a medication (Marsh, 2023). An adverse drug reaction is characterized as a response to a medication that is harmful and unintended, occurring at typical therapeutic doses. There is an underlying relationship between a medicine and an adverse drug reaction in contrast to an adverse event which does not necessarily have an underlying relationship with the medicine (Nebeker *et al*., 2004).

The terms' adverse reaction and adverse effect are essentially synonyms, with a slight distinction: an adverse effect is perceived from the drug's perspective, whereas an adverse reaction is viewed from the patient's standpoint (Edwards & Aronson, 2000).

The term adverse drug reaction will be used in this research report to refer to chemotherapeutic toxicity experienced by patients who receive chemotherapy to treat early-stage breast cancer.

1.4.2 Adverse drug reactions

Drug-induced mortality is a significant public health concern, as some countries spend 20% of their healthcare budget to manage adverse drug reactions (Ghai *et al*., 2021). An adverse drug reaction (ADR) is harmful and unplanned and happens at doses typically used for prevention, assessment, or treatment. The incidence of chemotherapy-induced adverse drug reactions (ADRs) ranges from 60-80% (On *et al*., 2022), and recent studies estimate that ADRs are the fourth to sixth leading contributors to mortality (Ghai *et al*., 2021). Adverse drug reactions lead to reduced quality of life and alterations in treatment plans like delays between cycles or reduction of cycles and dose (Han *et al*., 2011). Adverse drug reactions include nausea and vomiting, blood and lymphatic system disorders, hand-foot syndrome, fatigue, hypersensitivity reactions, gastrointestinal adverse effects, adverse neurological effects, and myelosuppression (Han *et al*., 2011; On *et al*., 2022). The type of ADR depends on the chemotherapeutic agent and the dose thereof, number of cycles administered, history of chemotherapy induced ADRs, comorbid disease, health status, age, and genetics (On *et al*., 2022).

1.5 Reporting of chemotherapeutic toxicity

1.5.1 Pharmacovigilance

Pharmacovigilance is a dynamic procedure for evaluating the safety of a pharmaceutical product throughout its entire lifespan (WHO, 2024). It commences in the preclinical development phase, persists throughout premarketing clinical trials, and extends into the post-market environment. Post-marketing safety monitoring is a mandatory obligation for marketing authorization holders. This involves implementing a transparent pharmacovigilance system, strict reporting duties to regulatory authorities in cases of significant safety issues, and submitting regular safety update reports (Cooper *et al*., 2024).

Past studies have demonstrated that ADRs are linked to significant financial implications, particularly concerning expenses associated with hospitalisation (De Rosa *et al*., 2020). The goal of pharmacovigilance is to prevent adverse events related to treatments (Schlam *et al*., 2023).

1.5.2 VigiAccess adverse drug reaction database

The World Health Organisation (WHO) introduced VigiAccess in 2015 to grant public access to information stored in VigiBase, the global database managed by WHO for reported potential adverse effects of medicinal products. VigiAccess is an online tool designed to facilitate searches within VigiBase, enabling users to retrieve condensed statistical summaries of the data related to potential adverse effects reported to the WHO Programme for International Drug Monitoring (PIDM). VigiBase, the exclusive worldwide database for reported potential adverse effects of medicinal products, has accumulated information since 1968 from members of the WHO PIDM. ADRs are reported to the WHO PIDM by national pharmacovigilance centres or regulatory authorities in member countries. The WHO PIDM, established in 1968 to ensure the safe and efficient utilization of medicinal products, saw South Africa become a member in 1992 (WHO, 2024).

1.6 Short-term adverse drug reactions (ADRs)

1.6.1 Nausea and vomiting

Nausea ranks among the predominant adverse effects of chemotherapy in breast cancer patients, and it is considered a more distressing symptom compared to vomiting. Breast cancer patients frequently undergo chemotherapy-induced nausea and vomiting (CINV) due to the presence of highly emetogenic agents in breast cancer chemotherapy. Notably, almost half of patients undergoing chemotherapy have reported experiencing CINV, even when using antiemetic medications (Wicaksono *et al*., 2023). Breast cancer chemotherapies are potent triggers of nausea and vomiting, which are perceived as the most upsetting and severe ADR. Despite significant advancements in managing acute chemotherapy-induced vomiting, as well as anticipatory and delayed nausea and vomiting, these adverse effects remain notable challenges for individuals with breast cancer. CINV persist as a common adverse effect that can significantly impact the lives of breast cancer patients. Adhering closely to antiemetic guidelines can help reduce the incidence of CINV. Despite strict adherence, breakthrough or refractory CINV may occur, necessitating further medical assessment. Despite substantial

therapeutic progress in the last forty years, 60% to 80% of patients still experience CINV during chemotherapy (Gautam *et al*., 2023).

1.6.2 Venous thromboembolism

Breast cancer is linked to a heightened risk of venous thromboembolism (VTE), including conditions such as pulmonary embolism and deep vein thrombosis. In contrast to individuals without cancer, those diagnosed with cancer face an 8-9 times higher risk of VTE within the first year of cancer diagnosis. The presence of cancer along with VTE is linked to a threefold increase in the risk of mortality. While the risk of VTE in breast cancer is comparatively lower than in many other solid tumours, the substantial prevalence of breast cancer makes breast cancer-associated thrombosis a significant health concern. Following cancer progression, VTE stands as the second most prevalent cause of death among patients undergoing chemotherapy for cancer, contributing to around 10% of deaths associated with chemotherapy (Kirwan and Blower, 2022). The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol 20 trial documented a thrombosis occurrence of 1.9% among patients in the tamoxifen treatment group, compared with 7.5% in those receiving tamoxifen plus a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) treatment group. A Canadian trial found similar results with a thrombosis incidence of 2.6% in the tamoxifen treatment group compared to 13.6% on the tamoxifen plus CMF treatment group (Partridge *et al*., 2001).

1.6.3 Alopecia

Alopecia is a frequent, distressing (Vasconcelos *et al*., 2018) adverse drug reaction of chemotherapy. The estimated occurrence is 65% in individuals undergoing treatment. Alopecia typically begins 1 to 3 weeks after the start of chemotherapy, reaches full effect by eight weeks, and hair regrowth is anticipated within 3 to 6 months after the completion of treatment (Fonia *et al*., 2017). Alopecia is frequently seen with anthracycline-based regimens and is more pronounced compared to non-anthracycline-based regimens (Partridge *et al*., 2001).

In a study by Partridge *et al.* (2001), the most frequently reported adverse effects reported for a combination of CMF included nausea, alopecia (partial hair loss), thrombocytopenia, vomiting, diarrhoea, and mucositis (Partridge *et al*., 2001). Adverse effects most frequently

reported for a combination of Doxorubicin and Cyclophosphamide (AC) included nausea, moderate to severe neutropenia, vomiting and mucositis (Partridge *et al*., 2001).

1.6.4 Fatigue, sleep disturbances and mood disorders

Breast cancer patients undergoing chemotherapy also experience cancer-related fatigue, sleep disturbances, and a depressed mood. These symptoms have been documented to occur in 68%–90%, 54%–78%, and 58%–79% of patients with breast cancer, respectively (Wong *et al*., 2023).

1.7 Long-term adverse drug reactions

1.7.1 Cardiovascular toxicity

The use of chemotherapy has been associated with persistent adverse effects, particularly cardiovascular conditions. Conditions such as hypertension, heart failure, and myocardial ischemia are common complications following the administration of chemotherapy (Alimperti *et al*., 2023). Cardiotoxicity impacts around 30% of patients (Langeh *et al*., 2023).

Doxorubicin is classified as an anthracycline and is a critical component in the chemotherapy regimen for breast cancer. Nevertheless, its application is restricted due to the cumulative and dose-dependent risk of irreversible cardiotoxicity (Zhao *et al*., 2023). The cardiotoxic effects associated with anthracycline begin with damage to myocardial cells, leading to subsequent left ventricular dysfunction. Anthracyclines trigger an elevated generation of free radicals and iron ions within cardiomyocytes, resulting in processes such as apoptosis induction and lipid bilayer damage (Pestana *et al*., 2024).

Data from Surveillance, Epidemiology and End Results (SEER)-Medicare indicate that older patients treated with anthracycline-based adjuvant chemotherapy face a heightened risk of cardiovascular events. Notably, many early breast cancer patients, particularly those with an elevated Body Mass Index (BMI), are more prone to future cardiovascular events than cancer recurrence (Tao *et al*., 2015). Reports indicate that up to 20% of patients may encounter cardiotoxic events such as QT interval prolongation, bradycardia, and atrial fibrillation following taxane administration (Alimperti *et al*., 2023).

Trastuzumab monotherapy can cause extensive reversible cardiotoxicity (Zhao *et* al., 2023) and also when combined with anthracyclines due to the HER2 pathway being a crucial part of cardiac homeostasis (Tao *et al*., 2015). Currently, older age, a low baseline left ventricular function (LVF), and a history of hypertension are recognised as contributing factors associated with an increased probability of cardiotoxicity from trastuzumab after anthracycline use. Consequently, many healthcare practitioners avoid anthracycline use altogether (Tao *et al*., 2015). Research conducted by Yu *et al*. (2015) revealed that around 10.90% of breast cancer patients discontinued anti-HER-2 therapy because of cardiac toxicity, potentially resulting in tumour recurrence.

1.7.2 Neurotoxicity

Adjuvant taxane regimens frequently cause adverse neurological reactions. The occurrence of grade 2-4 adverse effects ranges from 13% to 22% in sequential anthracycline-taxane treatments. Current findings suggest no correlation between toxicity and the probability of clinical advantages, allowing clinicians to decrease doses without compromising drug efficacy. Regrettably, there are few strategies to prevent or address the painful neuropathy induced by taxanes (Tao *et al*., 2015).

1.7.3 Cognitive function

Suter and Pagani (2018) reported that long-term adverse events of chemotherapy include cognitive impairment. Cancer-related cognitive impairment has been described as "chemo-brain," marked by impairment in memory function, decision-making abilities, and attention (Langeh *et al*., 2023).

Schagen *et al*. (1999) studied 39 women for about two years after receiving six cycles of CMF (with or without subsequent tamoxifen), comparing them with 34 women who underwent localized therapy only. The CMF group exhibited a higher incidence (28%) of cognitive dysfunction, primarily manifesting as difficulties in concentration, memory, word-finding, and motor skills testing, compared to the control group (12%). Interestingly, endocrine therapy did not impact self-reported symptoms or cognition.

A study by Van Dam *et al*. (1998) observed a dose-dependent relationship between chemotherapy and cognitive impairment. Two years after completing chemotherapy, 32% of patients treated with high-dose chemotherapy, 17% with standard-dose chemotherapy, and 9% of women with stage I breast cancer who did not undergo chemotherapy exhibited

impaired cognitive function. Brezden *et al*. (2000) surveyed 31 women undergoing chemotherapy, 40 previously receiving chemotherapy, and a healthy control arm. Women on active treatment exhibited more frequent impaired cognition compared to control subjects, which did not seem to be associated with anxiety or depression.

It's essential to highlight that, in the studies conducted by Van Dam *et al*. (1998) and Schagen *et al*. (1999), there was no correlation between self-reported cognitive dysfunction and formal testing scores. The women reporting poor cognition were not necessarily performing poorly on testing.

Decreases in cognitive performance on tests of memory, executive function, processing speed, and attention have been reported in several prospective longitudinal studies evaluating cognitive function before and after chemotherapy; 75% of patients experience these cognitive problems during treatment, and up to 35% of patients continue to be afflicted several years post-treatment (Janelsins *et al*., 2022). Janelsins *et al*. (2022) conducted a study to determine a relationship between inflammation and cognitive function pre- and post-chemotherapy in patients with breast cancer. This preliminary study sampled from a nationwide, longitudinal cohort of female breast cancer patients and age-matched non-cancer controls. Janelsins and colleagues (2022) discovered that Interleukin (IL)-6, MCP-1, sTNFRI, and sTNFRII, but not IL-1β or IL-8, increased during chemotherapy and that changes in these cytokines were associated with changes in cognitive function, particularly worse executive function, verbal memory, and verbal fluency.

1.7.4 Marrow neoplasm after adjuvant oncology chemotherapy

The occurrence of leukaemia after breast cancer was initially documented in the 1980s (Tao *et al*., 2015). The most severe long-term consequence of chemotherapy and radiation therapy is arguably the damage to hematopoietic stem cells, leading to secondary leukemia and myelodysplasia (Pullarkat *et al*., 2009). The increased rates of early tumour diagnosis and the effectiveness of adjuvant chemotherapy have significantly elevated the number of long-term survivors among cancer patients, enabling the detection of more long-term complications such as leukemias (Campone *et al*., 2005).

In the case of early-stage breast cancer, particularly when tumours exceed 1 cm in size, a majority of patients undergo adjuvant chemotherapy, typically involving cyclophosphamide and an anthracycline with or without a taxane. The development of secondary leukemia and myelodysplasia is a result of the damage inflicted on hematopoietic stem cells by

chemotherapy or radiation therapy and is considered a significant and potentially severe long-term consequence of these treatments (Pullarkat *et al*., 2009).

Curtis *et al*. (1992) conducted a case–control study involving nearly 82,700 women treated for breast cancer in the 1970s and 1980s. Their findings suggest that the total dose of Cyclophosphamide is a significant contributing factor for the development of leukaemia and myelodysplastic syndrome (MDS). Higher doses or dose-dense regimens of cyclophosphamide and doxorubicin on the NSABP protocol B-22 and B-25, showed a higher incidence of leukaemia and MDS, ranging from 0.1% to 1.2% (Campone *et al*., 2005). Cyclophosphamide is associated with leukaemia development 4 to 7 years after exposure. On the other hand, topoisomerase inhibitors such as doxorubicin and epirubicin, lead to leukaemia within 1-3 years (Campone *et al*., 2005) without a preleukemic phase, and the prognosis is relatively better than alkylating agent-associated leukaemia (Mirili *et al*., 2018).
Some evidence suggests that anthracycline-based treatment schedules may pose a bigger risk than traditional CMF regimens. The general occurrence of leukaemia among women with breast cancer following standard-dose adjuvant therapy using anthracyclines typically ranges from 0.1% to 1.5% within a 5 to 10-year follow-up period (Partridge *et al*., 2001).

1.7.5 Cessation of menses, menopause, and fertility

Adjuvant chemotherapy in premenopausal women often leads to early menopause. The risk of experiencing early menopause is associated with factors such as the patient's age, the chemotherapeutic agents used, and the total administered dose (Tao *et al*., 2015).

Typically, approximately 35% of women who undergo treatment with AC experience amenorrhea within 12 months after completing chemotherapy. This percentage rises to 45% for those who receive additional taxane treatment and rises to 60% for individuals treated with CMF. Generally, women under the age of 35 are more likely to regain their menstrual cycles fully, while those over 40 are less likely to do so (Tao *et al*., 2015). Among individuals under 40, menstruation typically resumes within one year after completing therapy in 90% of cases, while the percentage is slightly lower at nearly 70% for those over 40 (Langeh *et al*., 2023).

Although premature ovarian failure may have a positive impact on the breast cancer prognosis, especially for individuals with hormone receptor-positive tumours, premature menopause brings about symptoms like hot flashes and genitourinary issues. It can have significant physiological, psychosocial and psychosexual consequences (Partridge *et al*.,

2001). Women in early menopause experience quicker loss of bone mineral density. Nevertheless, women over the age of 35 face a higher risk of infertility when undergoing various adjuvant chemotherapy regimens, with rates ranging from 60% to 100% (Langeh *et al*., 2023).

1.7.6 Weight gain

Weight gain has been observed in most women undergoing adjuvant chemotherapy, with 33% of women gaining more than 5.0 kg (Lankester *et al*., 2001). Some researchers have reported more substantial weight gain, reaching 10–20 kg, in up to 20% of patients. This phenomenon seems more prevalent in women pre-menopause. Those women who are in menopause concurrently with chemotherapy seem to face an elevated risk of weight gain (Partridge *et al*., 2001). Gandhi *et al*. (2019) identified a lower initial BMI as the most robust predictor of substantial weight gain. Additionally, more significant weight increases were linked to CMF treatment compared to anthracycline therapy (Gandhi *et al*., 2019). Weight gain, especially when significant, can significantly impact a woman's physical and mental well-being (Partridge *et al*., 2001).

The exact reason for the increase in weight during chemotherapy remains unknown. Evidence proposes that reduced physical activity during therapy, potential fluctuations in basal metabolic rate, and a decline in muscle mass following chemotherapy may contribute to weight gain (Lankester *et al*., 2001).

1.8 Comorbidities amongst cancer patients

Comorbidity is defined as a disease present simultaneously and independently from the disease being studied (Newschaffer *et al*., 1997). According to Sreenivas on WebMD (2021), the most common comorbidities in the general population are high blood pressure, diabetes, cardiac disease, and respiratory disease. Curative treatments like surgery, radiotherapy, and chemotherapy may not be possible to perform or administer when the comorbidity involves a decline in organ function e.g., respiratory, cardiac, or renal function (Land *et al*., 2012).

The frequency of cancer rises with age and chronic diseases (Parés-Badell *et al*., 2017). In addition, most cancer patients have more than one comorbid condition which influence the timing of diagnosis by concealing the symptoms, leading to delayed consultation with a healthcare worker, which delays referral for further examination (Boakye *et al*., 2021). In

addition, comorbidities affect the choice and effectiveness of treatment options (Michalopoulou *et al*., 2021).

Cancer patients with comorbidities have a worse prognosis than those without comorbid conditions (Boakye *et* al., 2021). Increased mortality has been linked with comorbid diseases, but the presence of these comorbid diseases may have a different effect on mortality depending on the location of the cancer (Parés-Badell *et al*., 2017 and Michalopoulou *et al*., 2021). Patients with comorbid diseases use cancer treatment less often which affect cancer survival. Comorbidities also directly cause non-cancer death (Boakye *et al*., 2021).

On the other hand, patients with comorbid diseases visit healthcare workers frequently, which may result in increased chances of screening for cancer, leading to early detection and diagnosis (Boakye *et al*., 2021).

1.8.1 Demographic profiles of cancer patients and associated comorbidities

Age and gender factors

The National Cancer Institute in the United States released statistics that show that 54% of all cancer patients are 65 years and older. Sixty-one years is the mean age for breast cancer diagnosis (Stavrou *et al*., 2012). An estimated two-thirds of patients 65 years and older suffer from one or more comorbid diseases and take an average of four prescribed medications to manage these diseases (Stavrou *et al*., 2012).

More than 90% of patients aged 70 years and older have some comorbidity. Furthermore, 40% of these comorbidities are classified as severe (Kim *et al.*, 2019). Elderly patients often have a lower physiologic reserve, are functionally dependent on a caregiver, and have inadequate social support (Kim *et al*., 2019). Elderly patients also experience higher hospitalisation rates and adverse drug reactions from cancer treatment (McCleary *et al*., 2022). Older patients have a higher risk of experiencing treatment-related ADRs due to comorbidities and reduced organ function (Battisti *et al*., 2021).

Age should not impact the choice of systemic therapies (Suter and Pagani, 2018). Regrettably, older patients often face considerable difficulties with chemotherapy. Physicians are less inclined to recommend chemotherapy to older individuals, likely due to perceived lower tolerance, higher risks related to myelosuppression, and a perceived decrease in effectiveness

compared to younger patients. Furthermore, when provided with the choice, older women are less inclined to opt for chemotherapy, primarily due to concerns about potential subjective adverse effects like hair loss, nausea, and vomiting (Vogel *et al*., 1999).

Larger, more recent research provide evidence against the increased toxicity in older adults, despite a few smaller studies suggesting the opposite (Partridge *et al*., 2001). Crivellari *et al*. (2000) investigated the utilization of tamoxifen with adjuvant CMF in older women. While there was a larger hematologic and mucosal toxicity in women 65 years of age or older compared to younger women, quality of life evaluations indicated that the subjective treatment burden was similar for both age groups. In more recent prospective research, 44 women with early-stage breast cancer, ages 35 to 79, had adjuvant AC chemotherapy for four cycles. Myelosuppression was more severe in older women, although age did not substantially affect consequences such neutropenia, changes in cardiac function, or changes in quality-of-life scores (Dees *et al*., 2000).

When diagnosed with breast cancer, women under 40 years old have unique challenges, such as family planning, and fertility preservation. Young women should be offered genetic counselling, especially those with a family history of breast cancer (Suter & Pagani, 2018). Women under 40 make up less than 7% of all breast cancer patients in industrialized nations. The most common malignancy in women between the ages of 15 and 39 is breast cancer. In high-income nations, breast cancer ranks as the third leading cause of mortality for young women. Higher HER2 positive rates, greater triple-negative histology, and higher-grade hormone-responsive tumours might all account for this. Young women typically exhibit symptoms at the time of diagnosis because they are more likely to experience a delayed diagnosis due to diagnostic delays. One distinctive problem with screening in this population is that breast imaging has to be scheduled around the menstrual cycle. To lower the risk of false positives from functional contrast enhancement, breast MRIs and mammograms should be performed between days 5 and 12 of the cycle (Suter and Pagani, 2018).

Family planning is frequently incomplete in women under 40 years old, making fertility preservation a sensitive subject that should be addressed at the beginning of treatment. Pregnancy should be avoided while receiving active therapy for breast cancer due to the teratogenic risk of chemotherapeutic therapies. Proactive counselling is essential and should revolve around contraception discussions and addressing sexuality concerns, such as dyspareunia, vaginal dryness, and loss of libido. Medications like vaginal moisturisers or lubricants may be prescribed (Suter and Pagani, 2018). Additional challenges encompass

changes in body image, fatigue, and difficulties with shoulder and arm movements (Hopwood *et al.*, 2006).

Ethnicity profiles

The age distribution of breast cancer in South Africa exhibited an opposite trend compared to the rest of Africa. It mirrored the Caucasian age distribution in Europe. This could be partly due to the proportion of Caucasian residents in South Africa. However, in four of the seven South African studies where race was documented, 90% of the patients were black. It was not specified whether these patients were of mixed-race black descent (Olayide *et al*., 2021).
The overall lifetime risk of developing breast cancer (from birth to age 74) is one in 36, but this varies significantly across different racial groups. For black women, the risk is one in 81, while for white women, it is one in 13. Mixed-race women have a lifetime risk of one in 63, and Asian women (mainly of Indian origin) have a risk of one in 21. Breast cancer is less prevalent among black women compared to other population groups (Vorobiof *et al*., 2001).

Unique factors in the epidemiology of breast cancer for the black population include a slightly later age of menarche (14.7 years in rural black women and 13.9 in urban black women, compared to 12.6 in white women), an earlier age at first childbirth, high parity, and prolonged lactation. A demographic survey in South Africa found that 17.8% of black females aged 15 to 19 had ever been pregnant, compared to 2.2% of white females. Only 22% of black female patients presented with early-stage breast cancer (stages I and II), while nearly 69% of nonblack patients were diagnosed at these early stages. In contrast, stages III and IV were most prevalent among black women (77.7%) compared to nonblack women (30.7%) (Vorobiof *et al*., 2001).

Additionally, a study from Cape Town identified that a higher educational level, belonging to a medical aid fund or insurance, urban residence, and a family history of breast cancer were determinants of early-stage presentation (Hoffman *et al*., 2000).

1.8.2 Common comorbidities amongst cancer patients

Human Immunodeficiency Virus (HIV)

More than 40% of HIV-infected patients are anticipated to develop cancer during their illness (Hurley *et al*., 2001). On an international scale, studies exploring the association between HIV

infection and breast cancer have been scarce. Most data generated in developed countries have been derived from relatively small study populations, often comprising of only 20 patients, and have failed to establish any correlation between HIV infection and breast cancer (Ngidi *et al*., 2017). In South Africa (SA), where a few studies have been conducted with substantially larger populations, no increased incidence of breast cancer among HIV-positive individuals was observed (Ngidi *et al*., 2017). However, these studies did reveal that HIV-infected women tended to present at a younger age. Additionally, existing research suggests that cancer patients with HIV often have a worse prognosis than non-infected patients with comparable staging for the same disease. Additionally, they are more likely to be diagnosed with more serious illness (Ngidi *et al*., 2017).

Concerns arise among medical doctors and oncologists when combining combination antiretroviral therapy (ART) with chemotherapy. Given the possible overlap in toxicities, the effect of chemotherapy on immunological function, and the possibility of drug-drug interactions, these concerns are reasonable. Several combination antiretroviral therapies (ART) show toxicities such myelosuppression, neuropathies, nausea, and diarrhoea that are also frequent with chemotherapeutic agents (Deeken *et al*., 2012).

The metabolism of paclitaxel primarily involves Cytochrome (CYP) 2C8, CYP3A4, and CYP3A5. As such, higher plasma concentrations of paclitaxel may occur from co-administration of it with CYP3A4 inhibitors such as ritonavir. Adverse events such as myelosuppression, elevated liver function tests, and peripheral neuropathy can result from this elevation. CYP2B6 and CYP3A4 metabolise cyclophosphamide. Modulating CYP3A4 activity may impact neurotoxicity, with induction potentially increasing adverse events and inhibition minimising them. Fortunately, the CYP3A4 pathway is only used by 10% of the administered drug dose. Anthracyclines have minimal potential for drug-drug interactions during concurrent ART administration as doxorubicin is not metabolised by the CYP system. Protease inhibitors and chemotherapeutic medications that are metabolized by the hepatic cytochrome P450 3A enzyme family may interact to alter the toxicity and effectiveness of both drug groups. Drugs that interact with ART might be employed in chemotherapy for prophylaxis against opportunistic infections. Therefore, their use should be carefully considered and potentially adjusted (Bressan *et al*., 2021).

Ngidi *et al.* (2017) carried out a retrospective patient chart review of all breast cancer patients who underwent chemotherapy from January 2012 to December 2015 at the Inkosi Albert Luthuli Central Hospital and Addington Hospital in Kwa-Zulu Natal, SA. Among the most severe haematological toxicities linked to chemotherapy, neutropenia was the most notable.

The neutropenic episodes occurred at a ratio of 3:1 in HIV-infected individuals compared to uninfected patients. HIV-infected patients consistently exhibited a lower baseline absolute neutrophil count and mean white cell count than uninfected patients, which persisted throughout the chemotherapy cycles. The lowest absolute neutrophil count in the HIV-infected group was observed after the first chemotherapy infusion. In contrast, the lowest absolute neutrophil count in the non-infected group was noted after the second cycle of chemotherapy. Neutropenia and its complications were more prevalent among HIV-infected patients between cycles.

Notably, neutropenia brought on by chemotherapy was found to be independently predicted by HIV infection. This result implied that HIV-positive individuals were more likely to experience neutropenia because of comorbidities, myelosuppressive medications, and lowered immunity. As an alternative to dose reduction, growth factor support—specifically, granulocyte colony-stimulating factor (G-CSF), such as filgrastim—was recommended. This underlines that treating existing neutropenia with G-CSF is less advantageous than preventing it (Ngidi *et al*., 2017).

Gomez *et al*. (2015) conducted a retrospective patient file review of HIV-positive patients diagnosed with breast cancer at the University of Miami/Jackson Memorial Hospital in Florida, United States of America. Patients diagnosed between January 1, 1989, and December 31, 2013, were included. A comparison of the 48 consecutive HIV-infected breast cancer patients revealed that these patients were more likely to be younger and African American. Between 2006 and 2010, the median age of a diagnosis of breast cancer was 46, whereas the median age of the general population was 61. These HIV-infected breast cancer patients were younger than the median age for African American women without breast cancer (57 years). Among the 30 patients who received chemotherapy, 14 patients (46%) experienced serious adverse events. In ten patients, the primary complication was myelosuppression or neutropenic fever, leading to one fatality attributed to neutropenic fever. The main cause of death was breast cancer, and the mortality had a statistical relationship with the stage of the disease upon presentation. At five years, the overall survival rate for HIV-positive women with breast cancer was 57%, while the general population's rate was 89.2%, as reported by the SEER database for the years 2004–2010 (Gomez *et al*., 2015).

Diabetes

Diabetes is a common comorbidity in patients with solid tumours, and outcomes are generally worse for these patients (Sempere-Bigorra *et al*., 2021). For individuals with type 2 diabetes

mellitus, controlling daily lifestyle choices and maintaining blood pressure and glucose levels acceptable are essential to delaying the onset and progression of complications from the disease as well as atherosclerotic diseases (Terao and Suzuki, 2021).

Four to eighteen percent of diabetic cancer patients have hyperglycaemic events while receiving chemotherapy. Several factors contribute to hyperglycaemia: nutrition, less physical activity, stress, infection, old age, obesity, glucocorticoids, and chemotherapeutic agents. Hyperglycaemia increases the probability of suffering from chemotherapy-induced toxicities like neutropenia and neuropathy (Ahn *et al*., 2020).

Corticosteroids used for antiemetic and allergy prophylaxis during chemotherapy can cause hyperglycaemia in diabetic people. Terao and Suzuki (2021) compiled the findings from 13 trials that examined adverse effects in patients with diabetes who were receiving chemotherapy. During treatment, blood glucose levels were measured as high as 16.67 mmol/l. Within a few hours of starting chemotherapy, blood glucose levels began to rise, peaked at around 10 hours, and then started to decline after 24 hours. The day following therapy, the mean fasting blood glucose level rose dramatically from 7.3 ± 2 mmol/l before to 9.1 ± 2.9 mmol/l before breakfast. In the first round of chemotherapy, 80% of the 40 patients had hyperglycaemia. The cumulative dosages of dexamethasone were found to be significantly positively correlated with elevated HbA1c and blood glucose levels. Notably, blood glucose and HbA1c levels significantly increased with cumulative dosages of dexamethasone greater than 150 mg.

One common adverse effect of chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN), which can have a dose limit for a variety of chemotherapeutic drugs. Hyperglycaemia causes peripheral nerve damage, and for that reason, diabetic patients may have a greater risk of developing CIPN. The type of chemotherapeutic agent, the number of cycles, and the dose received play the most prominent roles in the occurrence of CIPN. Diabetic patients are more likely to experience neuropathy due to the loss of axonal integrity because of decreased regeneration (Sempere-Bigorra *et al*., 2021).

Sempere-Bigorra *et al*. (2021) found that peripheral neuropathy developed in 74.4% of diabetic patients during treatment with paclitaxel compared to 58.4% in patients without diabetes. The adverse effects seen by diabetes patients were substantially more severe; 51.2% of them had grade 2-3 toxicities, compared to 27.7% of non-diabetic patients. Additionally, individuals who have diabetes are more likely than non-diabetic patients to experience a delay in the resolution of CIPN. Female patients suffering from diabetes saw higher rates of chemotherapy delays

(20.9%) and dose reductions (32.6% vs. 11.9%) than females without diabetes (7.1%). (Sempere-Bigorra *et al*., 2021).

Bhatnagar *et al*. (2014) reviewed 123 medical records of breast cancer patients treated with sequential taxane between January 1, 2008, and December 31, 2011. Patients with diabetes had a two times greater likelihood of the taxane dose getting reduced. The study further demonstrated that dose reductions due to CIPN were more likely in patients receiving paclitaxel than docetaxel (Bhatnagar *et al*., 2014). Paclitaxel-induced peripheral neuropathy typically starts with numbness and paraesthesia (Sempere-Bigorra *et al*., 2021).

Peripheral nerve dysfunction was identified in 52% of individuals with diabetes for less than five years and 75% of patients with diabetes for more than five years, in trials with over fifty patients (Terao and Suzuki, 2021). The risk of new infections rose by 68% in patients with diabetes compared to those without the disease in a study involving patients who received intravenous chemotherapy with steroids. Furthermore, patients with diabetes had a 37.0% hospitalization risk for infection within the first year following initial treatment, compared to a 29.2% incidence for patients without diabetes. Chemotherapy with alkylating agents was found to be the main contributing factor to the development of infectious illnesses in these patients. Hospitalisations were primarily attributed to infection, neutropenia, and anaemia (Terao and Suzuki, 2021).

In a study by Terao and Suzuki (2021), oral mucositis caused by chemotherapy was noted in 5.9% of patients without diabetes and 6.9% of individuals with diabetes. Diabetes patients frequently have severe anorexia, nausea, and physical exhaustion. When individuals 66 years of age or older were receiving adjuvant chemotherapy for breast cancer, more individuals with diabetes (32.7%) than without diabetes (25.1%) were admitted to the hospital during the treatment. Diabetes was also found to be a predictor of heart failure among patients receiving chemotherapy for breast cancer (Terao and Suzuki, 2021).

Obesity

Obesity is a BMI of ≥30kg/m^2. The South African Demographic and Health Survey Report (2016) indicated that 31% of men and 68% of South African females are obese. Furthermore, one in five females have a BMI equal to or above 35kg/m^2 (National Cancer Strategic Framework, 2022). Obesity was previously perceived as an issue primarily affecting high-income countries. Prevalence however has increased notably in the urban areas of low- and middle-income countries (Furlanetto *et al*., 2016).

Diabetes, obesity, and cancer regularly co-occur. A study conducted in Sweden showed that obesity raised the probability of 15 different types of cancer, with Hodgkin lymphoma 5 in men having the highest standardised incidence ratio of 3.3. After a meta-analysis of 221 datasets, it was ascertained that the risk for common and rare malignancies increases with every 5kg/m2 increase in BMI (Mao *et al*., 2021).

Several factors may lead to a poorer prognosis due to obesity (Lomma *et al*., 2023), including delayed self-detection, delayed diagnosis, increased surgical and radiation treatment complications, decreased efficacy of hormonal treatments, underdosing systematic chemotherapy, and a decline in health-related quality of life (James *et al*., 2015).

Obesity is recognised as a significant public health issue and is linked to an elevated risk of chronic diseases and cancer (Furlanetto *et al*., 2016). Obesity has been correlated with various health issues, such as coronary heart disease, hypertension, cerebrovascular events, type II diabetes mellitus, osteoarthritis, and depression (Horowitz and Wright, 2015). In the case of females with breast cancer, obesity independently serves as a prognostic factor for the development of distant metastases and cancer-related deaths (Furlanetto *et al*., 2016). Obesity poses a high risk for vascular complications and early mortality in patients with diabetes. Oxidative stress, inflammation, and endothelial dysfunction cause organ damage in obese and hyperglycaemic patients (Mao *et al*., 2021). Patients with obesity tend to be diagnosed with more advanced diseases compared to non-obese counterparts (Furlanetto *et al*., 2016).

International guidelines advise chemotherapy doses based on actual body weight without capping or relying on ideal body weight, irrespective of a patient's body mass. Evidence suggests that obese patients receive lower chemotherapy doses despite these recommendations. A British investigation, discovered that 20% of obese individuals with early-stage breast cancer were given a dose cap. On the other hand, 70% of oncologists use either a capped dose or doses based on ideal body weight when administering chemotherapy to obese patients, according to Australian research covering all cancer types, which found that only 6% of physicians utilize actual body weight. Determining if individuals with obesity are at a higher risk of toxicity from medication is important because it can affect the efficacy of treatment when toxicity results in dose decrease or termination (Lomma *et al*., 2023).

To provide safe and effective cancer care for a growing percentage of the population, it is imperative to establish suitable dose strategies for chemotherapy in obese patients. Body Surface Area (BSA)-based dose calculations can result in very high doses. Concerned about

potential excess toxic effects, many practitioners reduce the chemotherapy doses given to obese patients. Some practitioners opt for calculating the dose based on ideal body weight (IBW) instead of actual body weight (ABW) when calculating BSA for obese patients, potentially resulting in a 25% reduction in chemotherapy compared to patients dosed with ABW. Finally, some healthcare professionals limit the total dosage of a medicine given to obese individuals or use a maximum BSA of $2.0m^2$ when administering chemotherapy (Hourdequin *et al*., 2013). The reduced efficacy noted in obese patients is often attributed to this reduction in chemotherapy dosage (Furlanetto *et al*., 2016).

Obese patients treated at adjusted doses experienced significantly lower rates of febrile neutropenia, thrombocytopenia, and thromboembolic events than those dosed on actual body weight in a retrospective analysis evaluating the association between obesity and toxicity from dose-dense or dose-intense chemotherapy in 555 obese patients. Nevertheless, regardless of dosage administration, there was no change in progression-free survival or overall survival when compared to individuals who were not obese. Furthermore, unrestricted dose in obese patients receiving neoadjuvant chemotherapy was linked to higher rates of pathological full response and better disease-free survival (Lomma *et al*., 2023).

In the Geriatric Assessment-Driven Intervention (GAIN) study conducted in Europe between August 2004 and July 2008, most obese patients received chemotherapy adjusted according to BSA. Notably, when obese patients received full dose-dense or intense dose-dense chemotherapy, a higher rate of toxicities was observed, particularly high-grade haematological toxicities. In the intense dose-dense ETC (epirubicin, paclitaxel, and cyclophosphamide) arm, obese patients were three times more likely to experience febrile neutropenia than non-obese patients despite G-CSF prophylaxis. Additionally, obese individuals receiving full dose-dense chemotherapy experienced twice as many high-grade thromboembolic events in the dose-dense EC-TX (epirubicin, cyclophosphamide, paclitaxel, and capecitabine) group as those getting modified dosages (Furlanetto *et al*., 2016).

Hypertension

African American breast cancer survivors suffer from a more significant number of comorbid conditions than non-Hispanic White survivors which causes a 42% greater likelihood of dying from breast cancer. Williams *et al*. (2020) studied the association between hypertension, a significant cardiovascular disease (CVD) risk factor and ethnicity among breast cancer survivors. The study was based on data from the National Health and Nutrition Examination

Survey (NHANES) from 1999 to 2014. Williams *et al*. (2020) reported that hypertension occurred 30% more in African American women than in white women after adjusting for demographic and health-related factors. Compared to white women, African American women were less likely to smoke and more physically active, yet a larger proportion of African American breast cancer survivors had diabetes or obesity. A 25% occurrence of hypertension was reported in obese African American women and a 37% occurrence in African American women who suffered from diabetes and obesity (Williams *et al*., 2020).

African American breast cancer survivors have a significantly higher risk of dying from cardiovascular disease (CVD) than their white counterparts, according to data from the National Cancer Institute's SEER database. The American Heart Association (AHA) reiterated this increased risk for CVD morbidity and mortality among African American breast cancer survivors. Hypertension and other preventable CVD risk factors may increase the cardiotoxic effects of chemotherapy (Williams *et al*., 2020).

Dyslipidaemia

A well-established risk factor for cardiovascular diseases is an unbalanced lipid profile, which is characterized by increased total cholesterol, decreased levels of triglycerides and low-density lipoprotein (LDL) cholesterol, and decreased levels of high-density lipoprotein (HDL) cholesterol, apolipoprotein A, and apolipoprotein B (Li *et al*., 2018).

From May 2016 to February 2017, Storph *et al*. (2019) conducted research in the female surgical ward and laboratory unit at the Cape Coast Teaching Hospital. Fifty-one patients with invasive ductal carcinoma and advanced breast cancer undergoing chemotherapy were included in their study. All lipid parameters increased, but only HDL values increased significantly throughout each treatment cycle in a steady manner ($p=0.054$). This observation correlated with earlier studies (Storph *et al*., 2019).

Alimperti *et al.* (2023) carried out research at a tertiary hospital in Athens involving women admitted to the oncology clinic. The study included individuals aged 18 years and above diagnosed with primary breast cancer who were undergoing chemotherapy following either a total or partial mastectomy. Their findings revealed that throughout chemotherapy for breast cancer, there is a notable rise in total cholesterol, LDL, and triglyceride levels, while HDL levels remained unchanged by the last cycle of chemotherapy (Alimperti *et al*., 2023).

Various chemotherapy medications can induce significant dyslipidaemia in breast cancer patients' post-chemotherapy. Anthracyclines like doxorubicin have been found to diminish the expression of the ABCA1 gene and apolipoprotein A1 in HepG2 cells, both of which play vital roles in HDL levels (Alimperti *et al*., 2023). The effectiveness of treatment regimens involving taxanes is limited by notable toxicities. Taxanes, particularly paclitaxel, significantly decrease HDL levels compared to breast cancer patients not undergoing chemotherapy (Alimperti *et al*., 2023).

1.9 Problem statement

Clinical findings have indicated that chemotherapeutic toxicity amongst breast cancer patients varies with patient-specific demographics. Furthermore, many patients requiring chemotherapy for breast cancer treatment, often present with comorbidities, such as diabetes, hypertension, and obesity due to lifestyle habits. There is limited literature available in the South African context, reporting on evidence of correlations between chemotherapeutic toxicities with varied demographic and comorbidity profiles of treated patients with stage 0-III breast cancer.

1.10 Aim and objectives of the study

This study aimed to determine a potential correlation between demographic profiles and the presence of pre-existing comorbidities on the chemotherapy-related adverse effects experienced by patients with stage 0-III breast cancer at a private oncology centre in Gauteng. Furthermore, the study aimed to compare the study findings in a South African context, with adverse effects currently recorded on the WHO VigiAccess Adverse Drug Reaction database for chemotherapeutic toxicities.

The aim of the study was achieved through undertaking the objectives listed:

a. To investigate the occurrence of chemotherapy-related adverse effects experienced by patients with stage 0-III breast cancer in relation to demographic profiles (age, gender, ethnicity) of sampled patient charts.
b. To determine specific pre-existing comorbidities frequently recorded in sampled patient charts for those receiving chemotherapy for stage 0-III breast cancer, and to investigate the correlation between chemotherapeutic toxicity experiences and patient comorbidities.

c. To investigate interventions that were applied to mitigate the experienced adverse effects of chemotherapy amongst patients with stage 0-III breast cancer (chemotherapeutic agent modifications, dose reductions, or premature discontinuation of chemotherapy).
d. To compare the adverse events reported in patient charts to the WHO VigiAccess Adverse Drug Reaction database for chemotherapeutic toxicities.

Chapter 2: Research methodology

2. Chapter overview

This chapter presents the research methodology used to conduct the study. It describes the study site, sampling, data collection and data analysis methods. The chapter also details the ethical considerations for the study.

Figure 2.1: Flow diagram outlining the phases undertaken in the study.

2.1 Study design

This study was a quantitative, retrospective (January 2018 to December 2019) descriptive cohort analysis of patient medical charts from a large, private, oncology centre in Gauteng, South Africa.

2.2 Study site

The study site was the Sandton Medical Oncology Centre. It is a large, well-established, private medical oncology practice located in Sandton, Johannesburg. Sandton is an affluent suburb. Most of the patients treated at the practice, reside in Gauteng. The minority of patients travel from nearby provinces e.g. Mpumalanga and North West to receive treatment at this practice. The majority of the patients seen at the practice is a member of a medical aid. The practice has four practising medical oncologists. The Sandton Medical Oncology Centre offers various services to its patients, including medical oncology, radiation therapy, psychosocial care, rehabilitation facilities and sub-acute wards. Types of cancer mostly treated at the centre include breast, ovarian, non-small cell lung cancer, colorectal and urothelial cancers.

2.3 Study population and sampling

Approximately 432 patients receive treatment at the Sandton Medical Oncology Centre each year for a number of cancer types. The Global Cancer Observatory (2021), estimated that 14.3% of South Africans of a diverse range in gender, age and ethnicity, were diagnosed with breast cancer in 2020. Based on these statistics, approximately 62 patients are diagnosed with breast cancer at the Sandton Medical Oncology Centre annually. The Raosoft online sample size calculator was used to determine the sample size of 54 patient charts (Raosoft, 2004).

$$\text{Sample size} = \frac{\frac{z^2 \, x \, p \, (1-p)}{e^2}}{1+(\frac{z^2 \, x \, p(1-p)}{N \, x \, e^2})}$$

Equation 2.1: Sample size formula
Where N = sample population size; z = statistical level of confidence (95%); p = expected proportion of the sample with particular characteristics (p = 0.5); d = margin of error (d = 0.05).

Inclusion criteria

Patient charts that were included in the study sample have been detailed below:

- diagnosis of stage 0, I, II, and III breast cancer from January 2018 to December 2019;
- undergoing chemotherapy;
- Age ≥ 18 years;
- All genders (male; female; other).

Patient charts retrieved and reviewed that were incomplete in terms of the study data collection tool were excluded from the study.

2.4 Data collection tool

The data collection tool (Appendix 1) was developed by the researcher, in relation to the correlations outlined in the objectives of the study. The objectives were to investigate whether specific patient demographics and their presenting comorbidities correlate with particular chemotherapeutic toxicity experiences and the interventions by oncologists to toxicities. The data collection tool was transcribed into REDCap® for easier and more timely data collection. The data collection tool consisted of five sections, namely patient demographic, disease and treatment information, chemotherapeutic toxicity experiences, and corrective actions taken in response. The data collection tool was designed with check-box options within each of these sections, except for situations where “other” was a selected option, whereby further information was to be recorded manually. Demographics necessary to draw correlations outlined in the study objectives were only listed in the tool. Disease information referred to both the current cancer status (HER2, oestrogen, progesterone), along with comorbidities. The treatment section focused on the chemotherapeutic regimen prescribed for breast cancer, with the chemotherapeutic toxicities section based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Resultant recourse applied by the oncologist in response to toxicity experiences included “yes” and “no” checkboxes, with an additional “other” section to specify fewer common interventions employed.

2.5 Study procedure and data collection

Upon approval of the study protocol (Appendix 2), receipt of ethical clearance (Appendix 3) and study site permission granted (Appendix 4), patient charts were reviewed in accordance with the sampling method and inclusion criteria parameters. Patient charts were accessed

from the archive room located in the Sandton Medical Oncology Centre and manually retrieved, with charts reviewed on-site. Patient charts were randomly selected and reviewed to select the patient profiles that meet the inclusion criteria. This process of random selection was followed until the sample size was met. Patient charts included in the study were allocated a file number for researcher identification purposes only. No direct patient identifiers (name, identity number, contact details) were recorded at any point in time. Required data was extracted from the patient charts and transcribed on the REDCap® data collection tool (Appendix 1). Data collected from patient charts at the study site was done so following ethical guidelines and Protection of Personal Information Act (POPIA) adherence. Once the sample size was reached, the data was transferred to Microsoft Excel for review, cleaning, and analysis. Data storage occurred on the researcher's laptop, along with an additional back-up, and was shared with supervisors. All devices used were password-protected, and the researcher kept the REDCap® registration and sign-in details confidential. No paper-based records or data were taken off the study site.

2.6 Data analysis

Data analysis consisting of percentage frequencies was calculated using Microsoft Excel. Descriptive analyses of the patient demographic characteristics with adverse effect profiles experienced were determined through pivot tables and recorded as percentages and frequencies. Furthermore, comorbidity prevalence was analysed in patients experiencing chemotherapeutic adverse effects. Chemotherapeutic toxicity reported in patient charts from the study site was compared with adverse drug reactions already documented in the WHO VigiAccess Adverse Drug Reaction database for each chemotherapy regimen. Data collected at Sandton Medical Oncology Centre was further compared with the type of reported potential adverse effects in the WHO VigiAccess Adverse Drug Reaction database. The ten most prevalent adverse effects in the WHO VigiAccess Adverse Drug Reaction were listed for each treatment regimen. In the cases where the adverse effects were not reported for the regimen, the adverse effects were listed for each chemotherapeutic agent that makes up the regimen.

Inferential statistical analysis was conducted using Stata software version 18 (Stata Corp., College Station, TX, USA). Age groups were categorized as follow: 30-39 years, 40-49 years, 50-59 years, 60-69 years, and >70 years. The two patients aged >80 years were included in the >70 years category to prevent skewing the data. Ethnic groups were categorized as follows: black, other, and white. Ethnic data was originally split up to specify Asian, Black, Coloured, Indian, Other, and White. During the data analysis the researcher took the decision

to use the “Other” category to additionally include Asian, Coloured, and Indian collectively. This is due to the Asian, Coloured, and Indian category sizes being too small to produce values that can be extrapolated to the population. The p-values for the age categories against the number of adverse effects were determined using the Kruskal-Wallis test. The p-values for the different ethnic groups against the number of adverse effects were determined using the one-way ANOVA test, as well as for the number of comorbidities against the number of adverse effects. The p-values were determined for the different age groups against the number of side effects experienced as well as the age groups against the number of comorbidities present at the time of breast cancer diagnosis. The p-values ≤0.05 were considered statistically significant.

2.7 Ethical considerations

An ethics application was submitted to the University of the Witwatersrand Human Research Ethics Committee (HREC) - Medical, before any data collection was undertaken, making use of the study protocol approved by the Faculty of Health Sciences Research Office at the University of the Witwatersrand (Appendix 2). Data collection only commenced following receipt of the ethics clearance certificate (Appendix 3) and study site permissions to access patient charts (Appendix 4).

Current research ethics guidelines established by the University of the Witwatersrand, Human Research Ethics Committee (HREC) – Medical, were read and applied throughout the research study. An accredited human research ethics short course was attended and completed, by both principal investigator and supervisors, as a requirement during the ethics clearance process (Appendix 3).

This study entailed the retrospective analysis of patient charts; therefore, no patient consent was needed, following ethics guidelines from HREC - Medical. Confidentiality of patient information collected was maintained throughout the study, through coding during data collection, to ensure patient information collected and documented remained anonymous. Patient charts also remained on-site.

All sources of information considered in this study were correctly referenced, with a plagiarism report run on all written work through Turnitin (Appendix 5).

Chapter 3: Results and Discussion

3. Chapter overview

This chapter presents the findings of the retrospective review of patient charts from the study site. It provides a detailed descriptive analysis of the results and discusses the implications of the findings for the practice, as well as compares findings with other literature and VigiBase.

3.1 Demographic profiles represented in patient charts

The demographic information of the patients reviewed during the retrospective analysis of patient charts has been summarised in Table 3.1. A total of 54 patients aged between 31-82 years of age, with stage 0-III breast and receiving chemotherapy were recorded, fulfilling the sample size calculation requirement. Fifty-three patients were female (98%), one patient was male (2%), and zero patients identified as “other” (0%). Similar findings were published by Herbst (2021), indicating that males account for 1-3% of South African cases of breast cancer.

Table 3.1: Demographic profile of the study participants (n=54)

Variable	Frequency (n)	Prevalence (%)
Gender		
Female	**53**	**98.0**
Male	1	2.0
Ethnicity		
Black	13	24.1
White	**31**	**57.4**
Other	10	18.5
Age at diagnosis (years)		
30-39	7	13.0
40-49	10	18.5
50-59	**16**	**29.6**
60-69	13	24.1
>70	8	14.8

*Bold = highest percentage frequency per variable.

Most of the study sample consisted of white patients (57.4%). This is in line with population data for Sandton where the majority of the population consists of white individuals. White

women have a 1 in 13 lifetime risk of developing breast cancer compared to black women who have a 1 in 81 lifetime risk (Vorobiof *et al*., 2001). According to Stat SA (2011), Sandton's population is composed of 48.8% white, 37.4% Black African, 11.1% Indian/Asian, and 2.5% coloured individuals. The difference in lifetime risk of developing breast cancer is reflected in the fact that a higher number of white women were diagnosed with breast cancer when compared with the population data (49.9%). The lower lifetime risk in black women is also reflected in the data – 24.1% of the study sample was black, but Sandton's population consists of 34.7% black individuals. As of 2022, the population of South Africa is approximately 60.6 million, with the majority being of black ethnicity (81%) (Cowling, 2023). The ethnic composition of the study sample does not reflect the ethnic distribution observed in the country. This could be due to fact that the state of health is shaped by numerous elements, among them being disparities stemming from the historical past of apartheid and the socio-economic standing of individuals, often delineated by racial divides. In South Africa, research has indicated that a significant portion of individuals who have access to private healthcare services belong to the white ethnic group (Singh *et al*., 2016). Since the study was conducted in a private healthcare facility, this disparity is clear in the ethnic composition of the patient base.

The most common age amongst the patients included in the study sample were 50-59 years (29.6%). Stats SA (2023) reported that breast cancer has the highest incidence in the 40-49, 50-59 and the 60-69 age group. Similar results were evident in the current study. A study by Jedy-Agba *et al.* (2016) reported that majority of the patients in their investigation were between the ages of 35 and 49 years at diagnosis, which is around 10-15 years younger than patients in wealthier nations. The age distribution of our study sample does not reflect the same findings as the study conducted by Jedy-Agba *et al.* (2016). This could be the case since, out of 83 publications included in a systematic review and meta-analysis by Jedy-Agba et al. (2016), only 16 of them had a direct bearing on the population of South Africa. There were 48 papers pertaining to research populations in Western Africa, and 19 articles regarding study populations in Eastern or Middle Africa. The statistics that were reviewed by Jedy-Agba and associates were also outdated. In 40 of the included studies, the diagnosis of breast cancer occurred in the year 2000 or later, with an average diagnosis made between 1960 and 2011.

3.2 Disease profiles represented in patient medical charts

3.2.1 Breast cancer staging and hormone receptor status of participants

With a mean age of 54 years, stage II breast cancer was identified in 48.2% of the patients. With a mean age of 55 years, 25.9% of the patients were diagnosed with stage I breast cancer, and another 25.9% with stage III breast cancer. No patients were diagnosed with stage 0 breast cancer (Table 3.2). Stage 0 was included in the data collection as it fits the definition of early-stage breast cancer, but it doesn't require treatment with chemotherapy and was therefore excluded from statistical analysis (Kurian *et al*., 2018).

Table 3.2 details the distribution of the stages of breast cancer and the hormone receptor status amongst patients. Most patients were oestrogen-positive (66.7%), progesterone-positive (57.4%), and HER2-negative (48.2%). The percentage of patients with triple-negative breast cancer (TNBC) was 22.2% (negative for oestrogen, progesterone and HER2). Patients with tumours that were oestrogen-negative reflected the lowest percentage, at 11.1%. According to data from the South African National Cancer Registry (SANCR), 60% of South Africans, regardless of race, are diagnosed with oestrogen receptor-positive breast cancer. The number of oestrogen-positive patients at the Sandton Medical Oncology Centre is consistent with this data (Joffe *et al*., 2018).

Approximately 15–20% of breast cancers exhibit amplification or overexpression of the HER2 oncogene globally (Brewster et al 2014). A slightly higher percentage of HER2-positivity were reported at Sandton Oncology (29.6%).

Table 3.2: Profile of the cancer status of patients included in the study sample (n=54)

Variable	Frequency (n)	Prevalence (%)
Breast cancer stage		
0	0	0.0
I	14 (mean age: 55)	25.9
II	**26 (mean age: 54)**	**48.2**
III	14 (mean age: 58)	25.9
Hormone receptor status		
Oestrogen-positive	**36**	**66.7**
Oestrogen-negative	6	11.1
Progesterone-positive	31	57.4

Progesterone-negative	11	20.4
HER2-positive	16	29.6
HER2-negative	26	48.2
Triple-negative	12	22.2

*HER2 = Human Epidermal Growth Factor Receptor 2; Bold = highest percentage frequency per variable.

Women of African descent have been found to face an elevated risk of TNBC, often characterized by an earlier age of onset compared to other breast cancer subtypes (Arnold et al 2022). This correlates with the data collected at Sandton Oncology, where 38.5% of the black patients were diagnosed with TNBC compared to 19.4% of the white patients. A 2014 review suggests that two-thirds of tumours in black sub-Saharan African females are oestrogen-receptor positive (Jedy-Agba, 2016). Only 53.8% of patients of black ethnicity in this study were oestrogen-receptor positive. South Africa has its own unique demographic composition which can significantly differ from other countries in Sub-Saharan Africa. The sample size from this study is too small to adequately compare data relating to the tumour characteristics to that of other countries. Figure 3.1. represents the distribution summary of ethnicity versus hormone receptor profile of study participants.

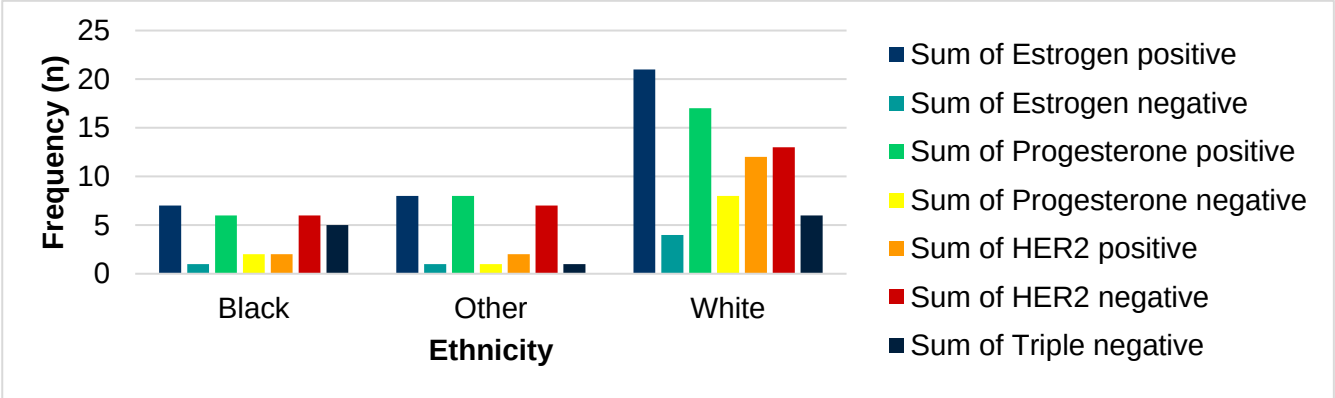

Figure 3.1: Representation of the ethnic distribution versus the hormone receptor status of the study sample.

3.2.2 Specific comorbidities frequently presented

Figure 3.2 further represents the number of patients according to the stage of cancer, ethnic group and the number of comorbidities the patient had at the time of diagnosis with early-stage breast cancer.

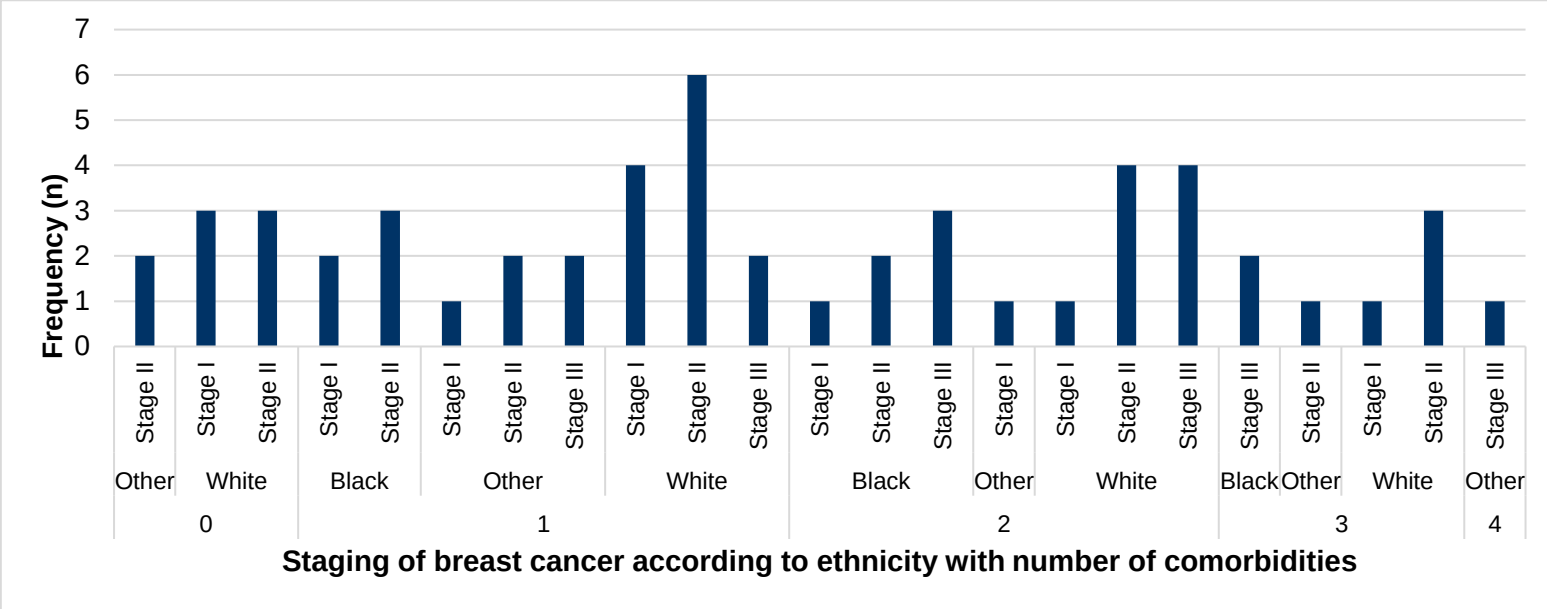

Figure 3.2: Stage of breast cancer and number of comorbidities shown per ethnic group.

White patients had 57.4% of the comorbidities at the time of diagnosis with black patients experiencing 24% of the comorbidities. Patients with zero or one comorbidity were most often diagnosed with Stage II breast cancer. Patients with two comorbidities were most often diagnosed with Stage III breast cancer. Table 3.3 provides further detail to the specific comorbidities represented by the study participants.

Ayeni *et al.* (2021) found that multimorbidity were associated with older age and higher socioeconomic status. Socioeconomic position was most often linked to the occurrence of chronic conditions. Women with higher socioeconomic position were more likely to be obese, diabetic, and hypertensive compared to women with lower socioeconomic position (Ayeni *et al*., 2021). 30% of individuals living in Sandton earns more than R 614, 001 annually (Stats SA, 2011). Earnings data for Sandton from the 2022 census in South Africa is not available. The difference in the number of comorbidities between white and black women could be due to disparities in the socio-economic standing of individuals, often delineated by racial divides in South Africa.

Table 3.3: Number of comorbidities experienced by the same patients (n=54).

Variable	Frequency (n)	Prevalence (%)	Comorbidities presented
0 comorbidities	8 (mean age: 48)	14.8	None
1 comorbidity	18 (mean age: 48.9)	33.3	Hypertension = 3 Dyslipidaemia = 1 HIV positive = 1 Underweight = 1 Obese = 2 Overweight = 10 Other = 2
2 comorbidities	17 (mean age: 59.4)	31.5	Hypertension = 8 Diabetes = 3 Dyslipidaemia = 2 HIV positive = 1 Normal BMI = 1 Obese = 7 Overweight = 6 Other = 9
3 comorbidities	9 (mean age: 64.7)	16.7	Hypertension = 7 Diabetes = 4 Dyslipidaemia = 3 Normal BMI = 1 Obese = 3 Overweight = 3 Other = 6
4 comorbidities	2 (age: 70)	3.7	Hypertension = 2 Diabetes = 1 Dyslipidaemia = 1 Obese = 1 Overweight = 1 Other = 2

Figure 3.3 provides further differentiation to the “Other” category indicated in Table 3.3, in terms of the comorbidities represented within this category for study participants at the time of breast cancer diagnosis.

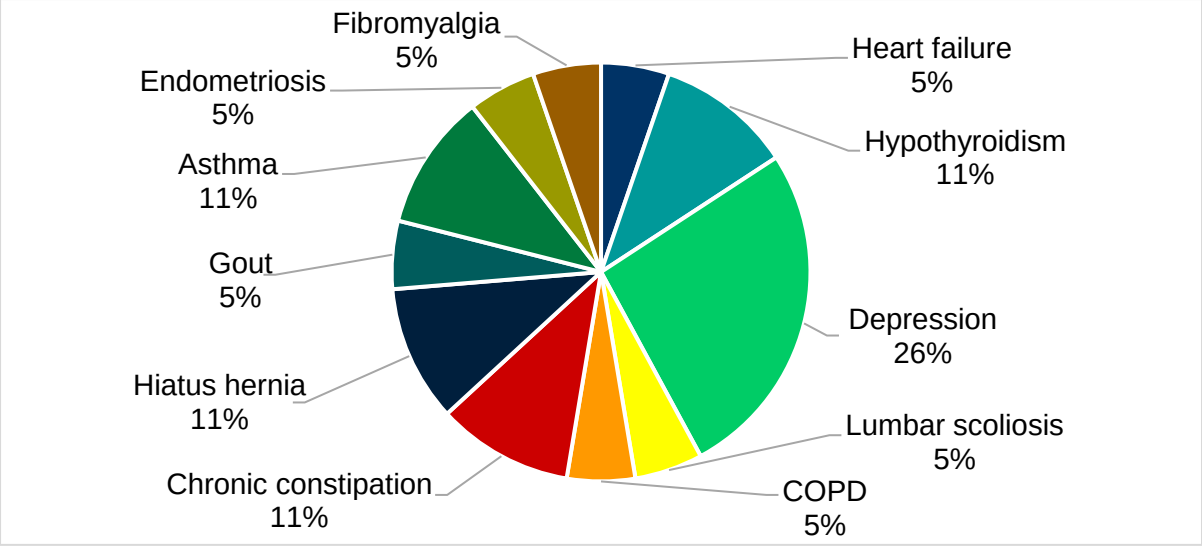

Figure 3.3: Other comorbidities listed in the patient charts of the study sample.

*COPD = Chronic obstructive pulmonary disorder; *Bold = highest percentage frequency per variable.

The BMI analysis of the patient group studied showed that most of the patients were overweight (37%) and only one patient was found to be underweight. For six patients, either the weight or height or both were not recorded to calculate the patients' BMI (Table 3.4).

Hypertension emerged as the most reported comorbidity across all age categories in studies focusing on specific types of comorbidities, followed by cardiovascular disease (CVD), diabetes mellitus, prior cancer, and chronic obstructive pulmonary disease (COPD) (Land *et al*., 2012). In addition to a high BMI, hypertension was found to be most frequently documented comorbidity amongst patients (35.2%) receiving oncology therapies at Sandton Oncology, with HIV least documented as a comorbidity amongst breast cancer patients (3.7%). The most common comorbidity was a BMI of 25-29.9. A 37% of patients were overweight. The second most frequent comorbidity was hypertension, with 35.2% of patients presenting with it. The third most frequent comorbidity was obesity (BMI>30), with 22.2% of patients presenting with it. The South African Breach Cancer and HIV Outcomes (SABCHO) prospective cohort study reported that the most common comorbidity was obesity (53%), hypertension (41%), HIV (22%), and diabetes (13%) (Ayeni *et al*., 2023). The SABCHO study was established to investigate survival determinants among HIV-positive and HIV-negative SA women with breast cancer (Mapanga *et al*., 2023). The difference in most common comorbidities between Sandton Medical Oncology Centre and the SABCHO study is attributable to the SABCHO study being a much larger study which is representative of the ethnic groups in the country. The data for the SABCHO data was collected from six government hospitals in South Africa while Sandton is an affluent suburb.

Table 3.4: Details of comorbidities seen in the patients.

Variable	Frequency (n)	Prevalence (%)
BMI		
Underweight (< 18.5)	1	1.9
Normal (18.5 - 24.9)	15	27.8
Overweight (25.0 - 29.9)	**20**	**37.0**
Obese (>30.0)	12	22.2
Unknown	6	11.1
Other common comorbidities**		
HIV positive	2	3.7
Diabetes	7	13.0
Hypertension	**19**	**35.2**
Dyslipidaemia	7	13.0
Other	19	35.2

*Bold = highest percentage frequency per variable ** Multiple responses.

The incidence of comorbidities rises notably with advancing age, starting at below 10% among breast cancer patients under the age of 50 and reaching 40% for those aged 80 or above (Ewertz *et al.*, 2017). As age increased, so did the quantity of comorbidities, along with the percentage of patients experiencing severe comorbid conditions (Land *et al.*, 2012). A similarity could be seen between the findings of Land and colleagues (2012) and the findings at Sandton Oncology: the number of comorbidities increased with the mean age, as demonstrated in Figure 3.4. This increase in comorbidities with age could be explained by the cumulative exposure to risk factors e.g. poor diet, sedentary behaviours, smoking, environmental exposures, and genetic predispositions; the biological aging process; or the progression of existing comorbidities e.g. patients with hypertension may develop CVD or kidney disease.

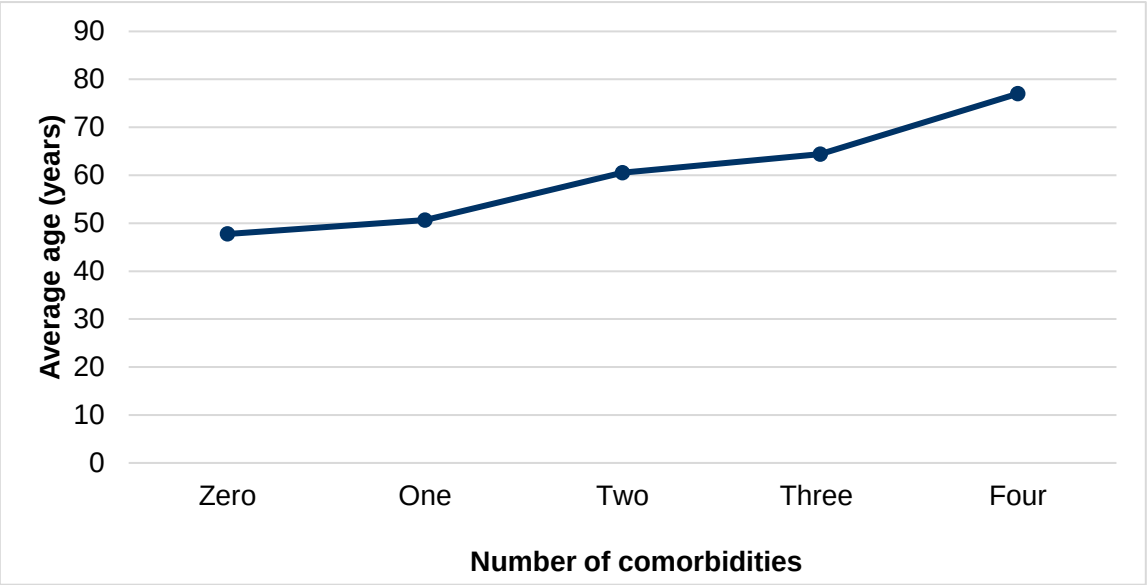

Figure 3.4: Average age versus number of comorbidities.

3.3 Treatment profiles for patients represented in the study sample

Only 7% of patients were treated with a taxane only (one with paclitaxel and three with a combination of docetaxel and cyclophosphamide); 5.5% of patients were treated with a taxane (paclitaxel) and trastuzumab; 51.8% of patients were treated with an anthracycline (doxorubicin or epirubicin) in combination with cyclophosphamide followed by sequential treatment with a taxane [docetaxel (5.5%) or paclitaxel (49.3%)]; 11.1% of patients were treated with an anthracycline in combination with cyclophosphamide [AC (7.4%) or EC (3.7%)] followed by sequential treatment with paclitaxel in combination with trastuzumab; one patient received a combination of a taxane, trastuzumab and pertuzumab, 9.3% of patients received TCH and 13% of patients were treated with CMF. A total of 51.9% of patients received neoadjuvant treatment. Of these 28 patients, 24 underwent radiation, and 26 underwent surgery. 48.1% of patients received adjuvant treatment. Of these 26 patients, 18 underwent radiation, and 25 underwent surgery (Table 3.5).

A vast 98.1% of patients included in this study received the first round of chemotherapy. One patient received the second round of chemotherapy (1.9%). All patients in the study reported ADRs from the chemotherapy. A majority of 77.8% of patients reported ADRs after receiving the first cycle of chemotherapy; 18.5% reported ADRs after receiving the second cycle of chemotherapy; one patient reported ADRs after receiving the third cycle of chemotherapy; and one patient reported ADRs after receiving the sixth cycle of chemotherapy (Table 3.5).

3.4 Practices employed to mitigate the experienced adverse drug reactions

A total of 32 corrective actions were implemented. One modification to the chemotherapeutic agent was made (3.7%), 19 dose reductions were implemented (70.4%), and twelve patients' treatments were discontinued (44.4%) (Table 3.5).

Table 3.5: Distribution of regimen prescribed and adverse effects experienced.

Variable	Frequency (n)	Prevalence (%)
Chemotherapeutic regimen prescribed		
Taxane-based	4	7.4
Taxane plus Trastuzumab	3	5.5
Anthracycline followed by taxane	**28**	**51.8**
Anthracycline followed by taxane and Trastuzumab	6	11.1
Taxane-Trastuzumab-Pertuzumab	1	1.9
TCH	5	9.3
CMF	7	13.0
Neoadjuvant treatment	28	51.8
Radiation	24	85.7
Surgery	**26**	**92.8**
Adjuvant treatment	26	48.2
Radiation	18	69.2
Surgery	**25**	**96.2**
The cycle of treatment at which adverse effects were recorded		
One cycles	**42**	**77.7**
Two cycles	10	18.5
Three cycles	1	1.9
Six cycles	1	1.9
Corrective action implemented		
Modification of agents used	1	3.7
Dose reduction implemented	**19**	**70.4**
Treatment terminated	12	44.4

* CMF = Cyclophosphamide, Methotrexate and 5-Fluorouracil; TCH = Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab); Bold = highest percentage frequency per variable.

3.4.1 Change of chemotherapeutic agent

The one modification to the chemotherapeutic agent used was a change from AC to a combination of docetaxel and cyclophosphamide (TC). The patient received one cycle of AC

at a different oncologist and was then changed to 3 cycles of TC when she started treatment at Sandton Medical Oncology Centre. The patient was a 60-year-old coloured female diagnosed with Stage I breast cancer. Hormone receptor status is oestrogen positive, progesterone positive and HER2 positive. She had two comorbidities, namely hypertension and diabetes. No reason for the change of chemotherapeutic agent was mentioned in the patient chart.

3.4.2 Dose reduction

Nineteen dose reductions were implemented in total. Most of the dose reductions were for patients who received an anthracycline followed by a taxane (68.4%). Most of the patients for which the dose was reduced were white (52.6%), had stage II breast cancer (63.2%), and had two and three comorbidities (31.6% and 31.6% respectively). An average of 5.5 different side effects were experienced by the patients for which the dose was reduced. Table 3.6 presents the physiological systems mostly affected by adverse effects that led to the dose reductions.

Table 3.6: Most prevalent adverse effects that led to dose reductions (n=19).

Affected system	Frequency (n)	Prevalence (%)	Adverse effect
Nervous	18	94.7	Neuropathy in hands and feet, fatigue, facial neuropathy, insomnia, headaches
Haematological	17	89.5	Neutropenia, leucopenia, lymphopenia, anemia, monocytosis, thrombosis, pancytopenia
Digestive	**15**	**79**	Constipation, nausea, vomiting, reflux, diarrhoea, mouth sores
Integumentary	14	73.7	Alopecia, rashes, itchiness

3.4.3 Termination of treatment

A limitation of this study was that the reason for termination of chemotherapy was not recorded during the data collection process e.g. disease progression, chemotherapy related toxicities, complete response to chemotherapy, or personal decision.

In 12 cases, the treatment was terminated, with 58.3% of the cases of treatment termination being preceded by dose reductions (Table 3.6).

Two patients were 40-49, 4 patients were 50-59, 2 patients were 60-69, 4 patients were >70. The average age of the patients for which treatment was terminated, was 62.8 years. Nine patients were diagnosed with Stage II breast cancer. Eight patients received an anthracycline followed by a taxane. Two patients received CMF. Four patients had two comorbidities at the time of diagnosis, and four patients had three comorbidities present. Two patients had four comorbidities.

Treatment was most often terminated in patients with Stage II breast cancer receiving an anthracycline followed by a taxane. An average of 4.8 different side effects were experienced by the patients for which the dose was reduced.

In patients over 70 years of age, dosage decrease rates (14%) and early discontinuation rates (23%) were observed by Brown *et al*. (2023). For example, a study assessing the administration of chemotherapy to patients 65 years of age and older discovered that 20% of patients stopped treatment early owing to toxicity and poor tolerance, and 9% of patients needed their dose reduced. According to another study, 21.3% of cancer patients over 65 stopped chemotherapy early owing to treatment-related toxicities, and more than half (55.6%) of these patients had treatment adjustments, such as delays or dosage reductions. In contrast, the rates of chemotherapy modification were lower in non-geriatric patients; just 5.1% of patients under 60 saw a dosage decrease, compared to 8.1% of those 65 and older (Brown *et al*., 2023). Furthermore, 26.3% of the dose reductions at Sandton Oncology were in patients aged 65 and older, whilst 41.7% of the treatment terminations at Sandton Oncology were in patients aged 65 and older. The number of patients older than 65 years that had dose reductions or treatment terminations were much higher that what was reported in the literature.

3.5 Adverse drug reactions at Sandton Oncology

Figure 3.5 represents the ADRs per physiological system that were most frequently documented in the patient charts.

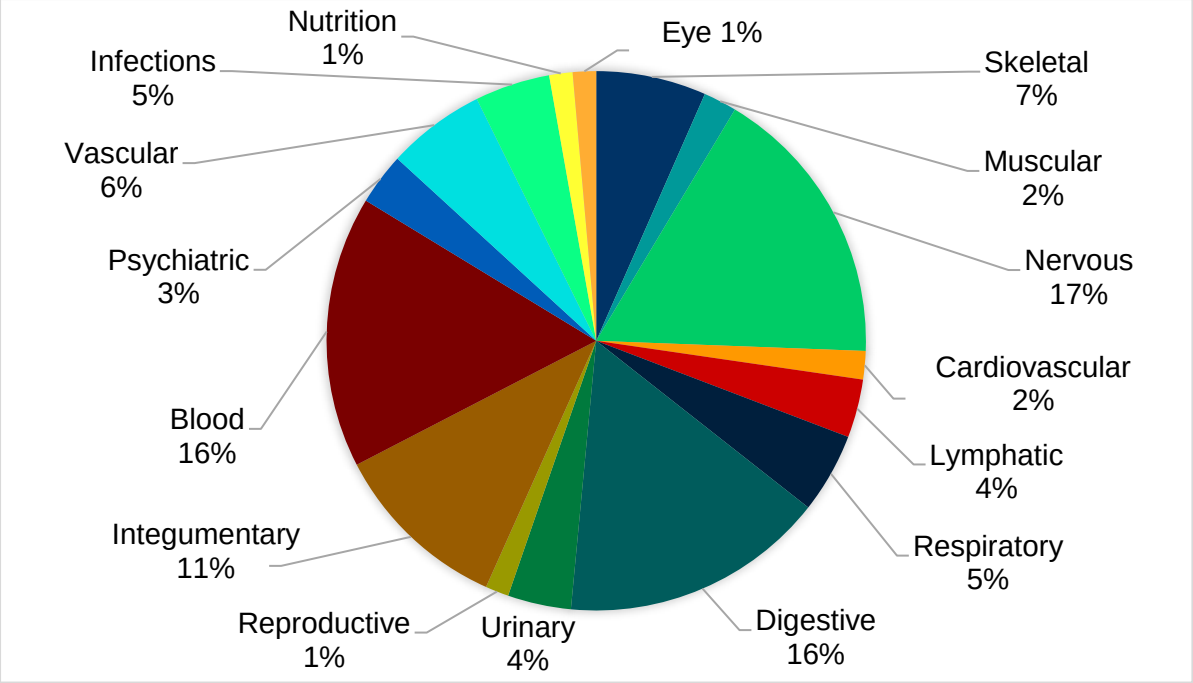

Figure 3.5: ADRs that were most frequently documented in relation to physiological systems.

In this study sample, the chemotherapeutic regimen with the highest average ADRs per patient, is the taxane-trastuzumab-pertuzumab combination. An average of 7 ADRs per patient was reported. Only one patient was treated with this combination and experienced 7 different ADRs. The chemotherapeutic regimen with the lowest average of ADRs per patient, is the taxane-based regimen. An average of 4.5 ADRs per patient was reported. Four patients were treated with a taxane-based regimen. Figure 3.6 presents the type of adverse effects experienced in patients treated with a specific treatment arm.

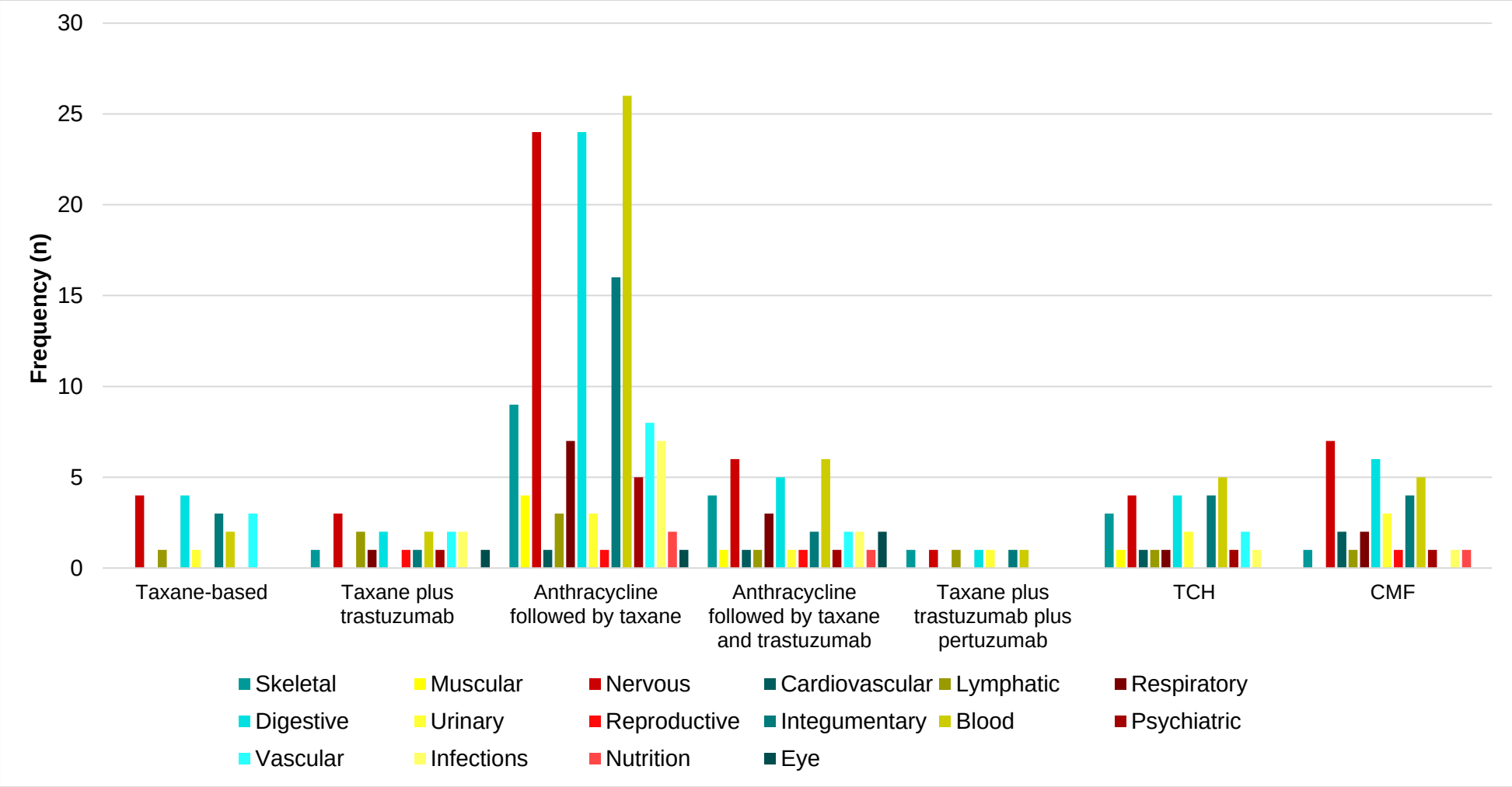

Figure 3.6: Types of adverse effects experienced specific to each treatment arm

* CMF = Cyclophosphamide, Methotrexate and 5-Fluorouracil; TCH = Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab).

The majority of patients across all ethnic groups received an anthracycline followed by a taxane (Figure 3.7).

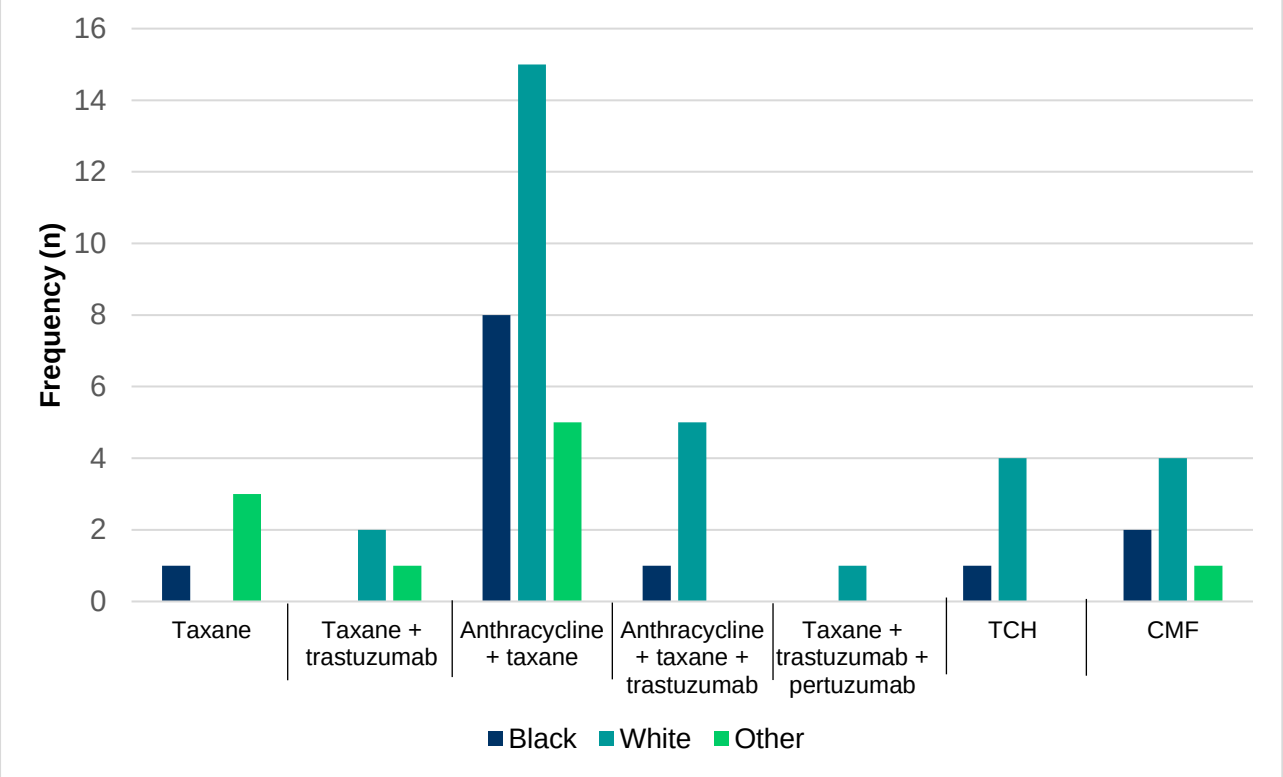

Figure 3.7: Ethnic distribution in each treatment arm

*CMF = Cyclophosphamide, Methotrexate and 5-Fluorouracil; TCH = Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab).

Many patients <70 years, received an anthracycline followed by a taxane (30-39 (71.4%); 40-49 (50%); 50-59 (68.8%); 60-69 (46.2%)). Most patients >70 years, received treatment with CMF (37.5%). This difference in treatment regimen between the age groups is due to changes in the way drugs are processed within the body due to age which influence the adverse effects of certain chemotherapy treatments in elderly patients. For instance, doxorubicin tends to accumulate more in older individuals due to slower distribution throughout the body's tissues, coupled with a decrease in clearance rate by approximately 9% for every 10-year increase in age (Crombag *et al.*, 2016). Although the impact of age on trastuzumab's effects is minor, it does play a significant role in reducing left ventricular ejection fraction (Brown *et al.*, 2023). Clinical observations indicate that individuals aged 70 and above receiving trastuzumab therapy have a higher risk of cardiotoxicity, particularly if they have a history of diabetes or cardiac issues, compared to those without such conditions (Brown *et al.*, 2023). This underscores the importance of considering comorbidities when selecting treatment approaches. Figure 3.8 presents the age distribution of the patients according to the treatment arms.

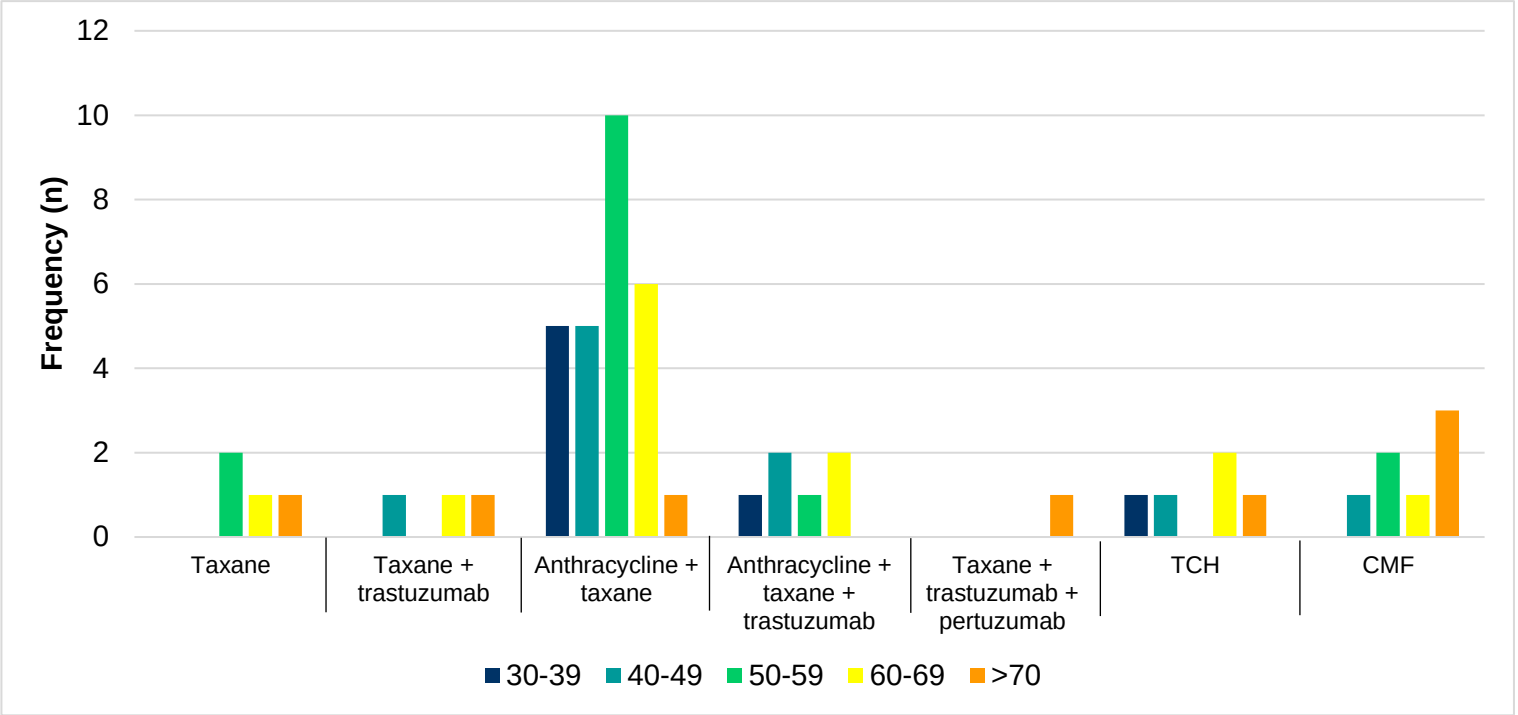

Figure 3.8: Age distribution in each treatment arm

*CMF = Cyclophosphamide, Methotrexate and 5-Fluorouracil; TCH = Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab).

3.6 The pattern of chemotherapy-related adverse effects in relation to age and ethnicity

White patients experienced the most adverse effects overall, except reproductive system adverse effects. No statistically significant correlation was found between any of the ethnic groups and the total number of adverse effects experienced. A statistically significant difference was initially observed between ethnic groups (p=0.03) in terms of adverse effects experienced. However, upon conducting the Bonferroni test to correct for multiple comparisons, no statistical difference was found between the number of black and white patients who experienced adverse effects (p=0.058). No statistically significant correlation was found between any of the age groups and the total number of adverse effects experienced.

Table 3.7: Mean, standard deviation (SD), interquartile range (IQR) and p-values for age, ethnicity and the number of comorbidities.

Measures	p-value	Frequency (n)	Mean ± SD	IQR
Age				
30-39 years	0.780	7		35.0 (33-38)
40-49 years		10		43.5 (41-46)
50-59 years		16		54.0 (52.5-55)
60-69 years		13		63.0 (61-67.5)
>70 years		8		77.0 (74-79.5)
Ethnicity				
Black		13	4.6 ± 1.9	
White		31	5.8 ± 1.4	
Other		10	4.8 ± 1.1	
Between groups	0.032			
Black vs white	0.058			
Black vs other	1.000			
White vs other	0.200			
Number of comorbidities				
Zero		8	4.9 ± 1.4	
One		18	5.9 ± 1.3	
Two		17	4.8 ± 1.5	
> Three		11	5.5 ± 1.9	
Between groups	0.115			
One comorbidity vs no ADRs	0.625			
Two comorbidities vs no ADRs	1.000			
>Three comorbidities vs no ADRs	1.000			
Two comorbidities vs one ADR	0.156			
>Three comorbidities vs one ADR	1.000			
>Three comorbidities vs two ADRs	1.000			

Table 3.8: Correlations for comorbidities against the number of adverse effects per physiological system.

Comorbidity	ADR	p-value	Comorbidity	ADR	p-value	Comorbidity	ADR	p-value
Hypertension	Skeletal	1.0000	Dyslipidaemia	Skeletal	0.4001	HIV positive	Skeletal	1.0000
	Musculoskeletal and connective tissue disorders	1.0000		Musculoskeletal and connective tissue disorders	1.0000		Musculoskeletal and connective tissue disorders	1.0000
	Nervous	1.0000		Nervous	1.0000		Nervous	0.1782
	Cardiac disorders	1.0000		Cardiac disorders	0.5150		Cardiac disorders	0.5150
	Lymphatic	0.2966		Lymphatic	**0.0171**		Lymphatic	1.0000
	Respiratory	0.3310		Respiratory	1.0000		Respiratory	1.0000
	Digestive	0.4309		Digestive	0.2747		Digestive	0.2767
	Urinary	1.0000		Urinary	0.1404		Urinary	0.6213
	Reproductive	1.0000		Reproductive	1.0000		Reproductive	0.1440
	Integumentary	0.1492		Integumentary	0.6854		Integumentary	1.0000
	Blood	0.4001		Blood	0.2205		Blood	0.2205
	Psychiatric	0.1369		Psychiatric	1.0000		Psychiatric	1.0000
	Vascular	0.7599		Vascular	1.0000		Vascular	0.5346
	Infection	**0.0427**		Infection	0.3399		Infection	1.0000
	Nutrition	0.6068		Nutrition	1.0000		Nutrition	0.0771
	Eye	0.1195		Eye	0.4360		Eye	0.4360
Diabetes	Skeletal	0.0572	Other	Skeletal	0.0916	Normal BMI	Skeletal	0.5320
	Musculoskeletal and connective tissue disorders	1.0000		Musculoskeletal and connective tissue disorders	0.2240		Musculoskeletal and connective tissue disorders	1.0000
	Nervous	0.5150		Nervous	0.3729		Nervous	0.6099
	Cardiac disorders	0.5150		Cardiac disorders	0.2458		Cardiac disorders	0.6099
	Lymphatic	1.000		Lymphatic	1.0000		Lymphatic	0.2515
	Respiratory	1.000		Respiratory	0.0406		Respiratory	0.4976
	Digestive	1.000		Digestive	1.0000		Digestive	1.0000
	Urinary	0.6213		Urinary	0.3543		Urinary	0.7076
	Reproductive	1.0000		Reproductive	0.6821		Reproductive	0.1379
	Integumentary	0.1223		Integumentary	0.3324		Integumentary	0.2200
	Blood	0.2205		Blood	0.7974		Blood	0.6586

Comorbidity	ADR	p-value	Comorbidity	ADR	p-value	Comorbidity	ADR	p-value
Diabetes	Psychiatric	1.0000	Other	Psychiatric	**0.0137**	Normal BMI	Psychiatric	1.0000
	Vascular	0.4026		Vascular	0.2453		Vascular	0.3379
	Infection	1.0000		Infection	0.5697		Infection	0.3112
	Nutrition	0.0771		Nutrition	0.4220		Nutrition	0.0771
	Eye	0.4360		Eye	0.2931		Eye	1.0000
Underweight	Skeletal	0.3519	Overweight	Skeletal	0.5723	Obesity BMI	Skeletal	0.3066
	Musculoskeletal and connective tissue disorders	0.1111		Musculoskeletal and connective tissue disorders	1.0000		Musculoskeletal and connective tissue disorders	1.0000
	Nervous	1.0000		Nervous	1.0000		Nervous	0.4292
	Cardiac disorders	1.0000		Cardiac disorders	1.0000		Cardiac disorders	1.0000
	Lymphatic	1.0000		Lymphatic	0.4714		Lymphatic	0.6745
	Respiratory	0.2593		Respiratory	1.0000		Respiratory	0.1517
	Digestive	1.0000		Digestive	0.6951		Digestive	0.3564
	Urinary	1.0000		Urinary	1.0000		Urinary	1.0000
	Reproductive	1.0000		Reproductive	0.1379		Reproductive	0.1379
	Integumentary	0.4259		Integumentary	0.0861		Integumentary	1.0000
	Blood	1.0000		Blood	1.0000		Blood	1.0000
	Psychiatric	1.0000		Psychiatric	0.7117		Psychiatric	1.0000
	Vascular	1.0000		Vascular	0.1335		Vascular	0.2998
	Infection	1.0000		Infection	0.5167		Infection	1.0000
	Nutrition	1.0000		Nutrition	0.0771		Nutrition	0.0771
	Eye	1.0000		Eye	1.0000		Eye	1.0000

3.6.1 Skeletal adverse drug reactions reported in patient charts

The age group 50-59 years experienced most of the skeletal adverse effects (e.g. bone aches), as demonstrated in Figure 3.9.

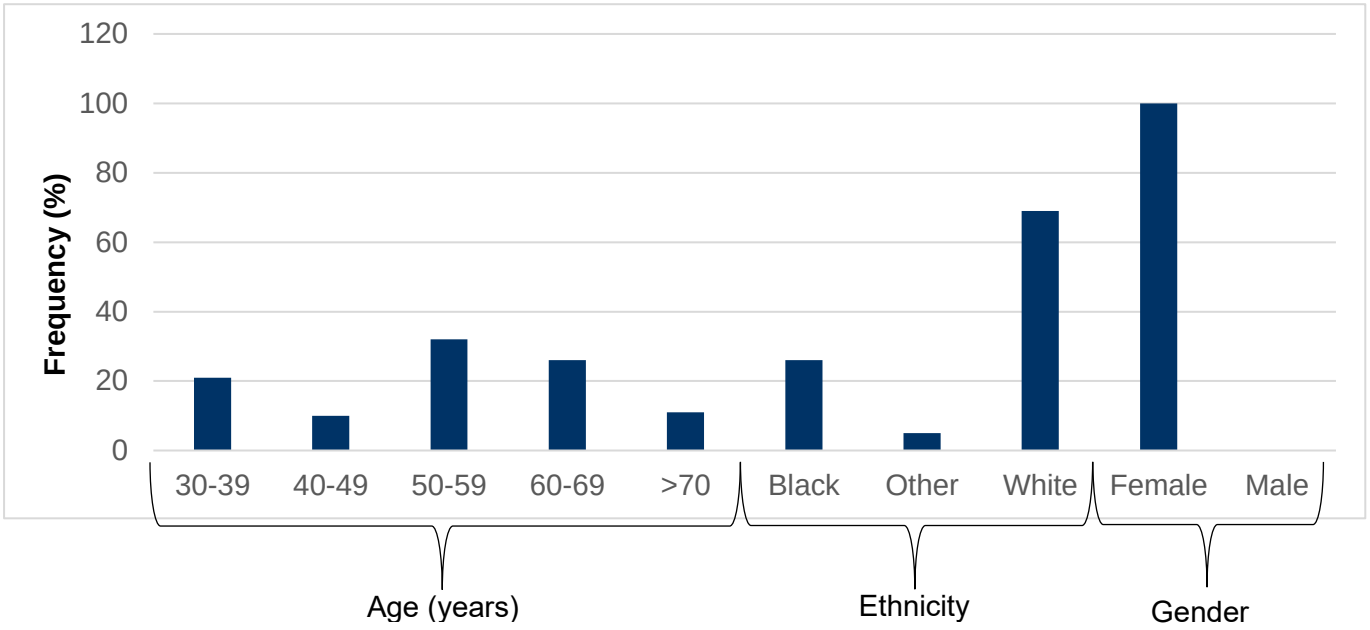

Figure 3.9: Age, ethnic and gender distribution of skeletal ADRs.

3.6.2 Muscular adverse drug reactions reported in patient charts

The age groups 40-49 years and 60-69 experienced the most muscular adverse effects (e.g. muscle pains in the back and shoulders), as demonstrated in Figure 3.10.

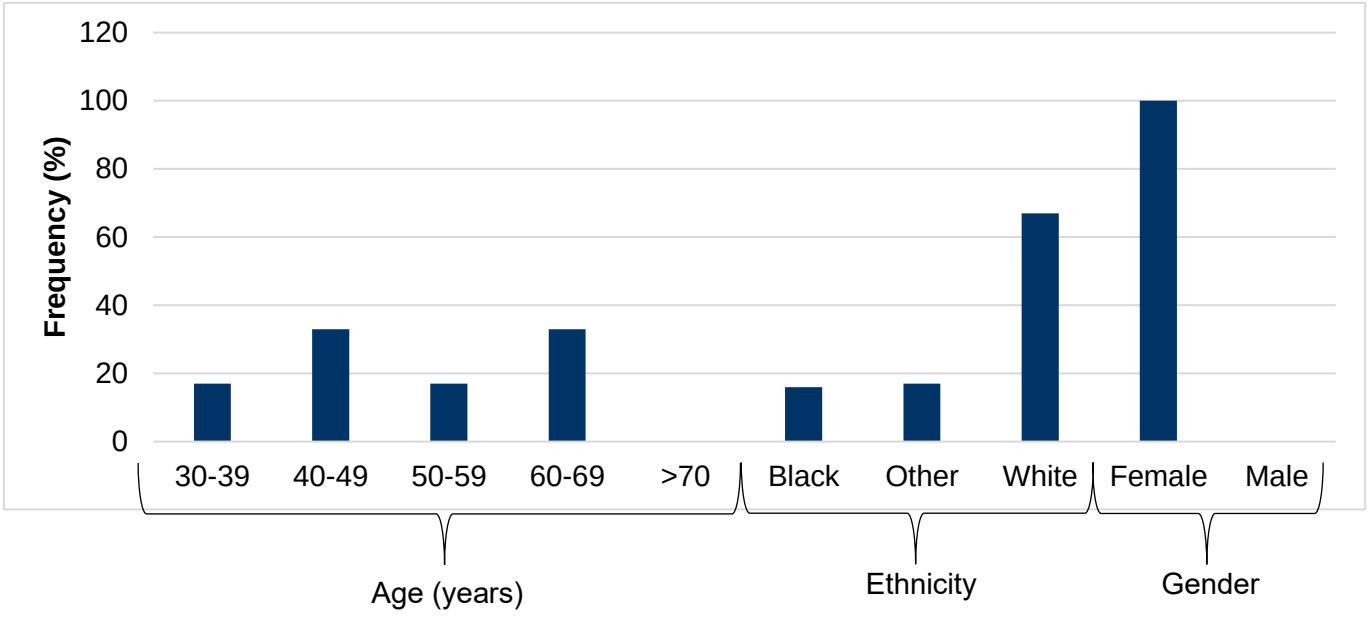

Figure 3.10: Age, ethnic and gender distribution of muscular ADRs.

3.6.3 Nervous system adverse drug reactions reported in patient charts

The age group 50-59 years experienced most of the nervous system ADRs (e.g. insomnia, fatigue, peripheral neuropathy, paraesthesia), as demonstrated in Figure 3.11.

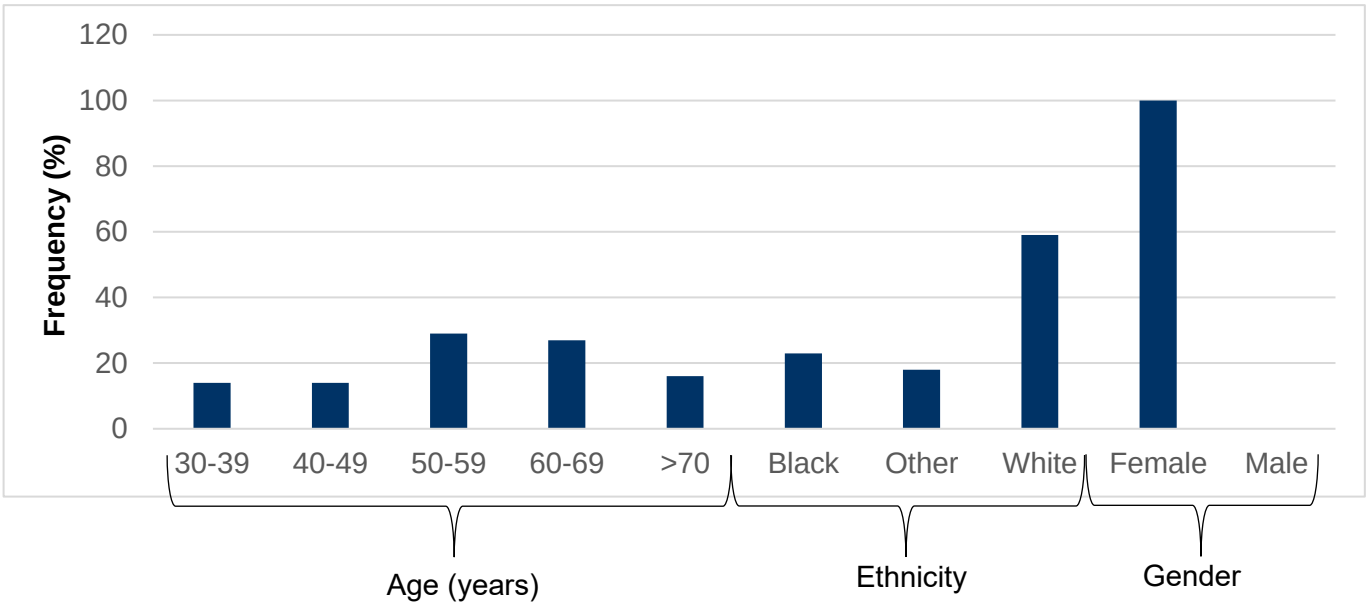

Figure 3.11: Age, ethnic and gender distribution of nervous system ADRs.

3.6.4 Cardiovascular system adverse drug reactions reported in patient charts

The age group 60-69 years experienced much of the cardiovascular system ADRs (e.g. tachycardia, elevated blood pressure) as demonstrated in Figure 3.12.

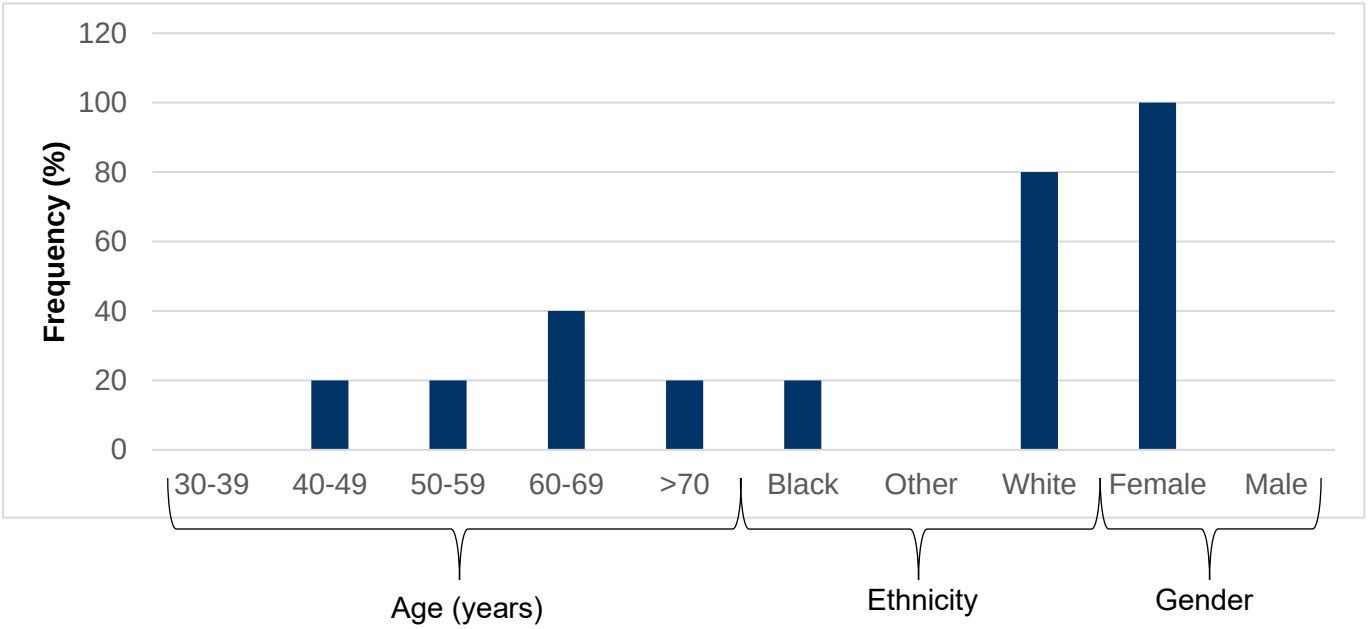

Figure 3.12: Age, ethnic and gender distribution of cardiovascular ADRs.

3.6.5 Lymphatic system adverse drug reactions reported in patient charts

The age group 70-79 years experienced the most lymphatic adverse effects like lymphedema and a swollen face, as demonstrated in Figure 3.13. A statistically significant correlation (p=0.017) was found between dyslipidaemia and the number of lymphatic system adverse effects.

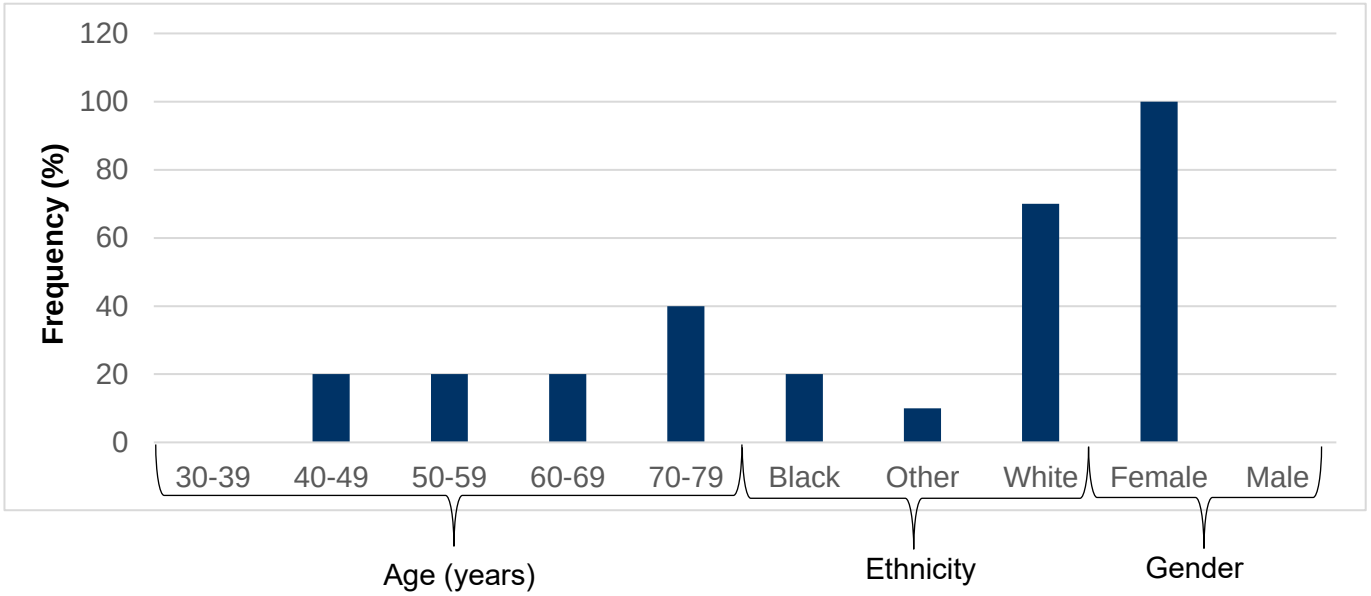

Figure 3.13: Age, ethnic and gender distribution of lymphatic ADRs.

3.6.6 Respiratory system adverse drug reactions reported in patient charts

The age group 50-59 years experienced most of the respiratory adverse effects (e.g. cough, congested sinuses), as demonstrated in Figure 3.14.

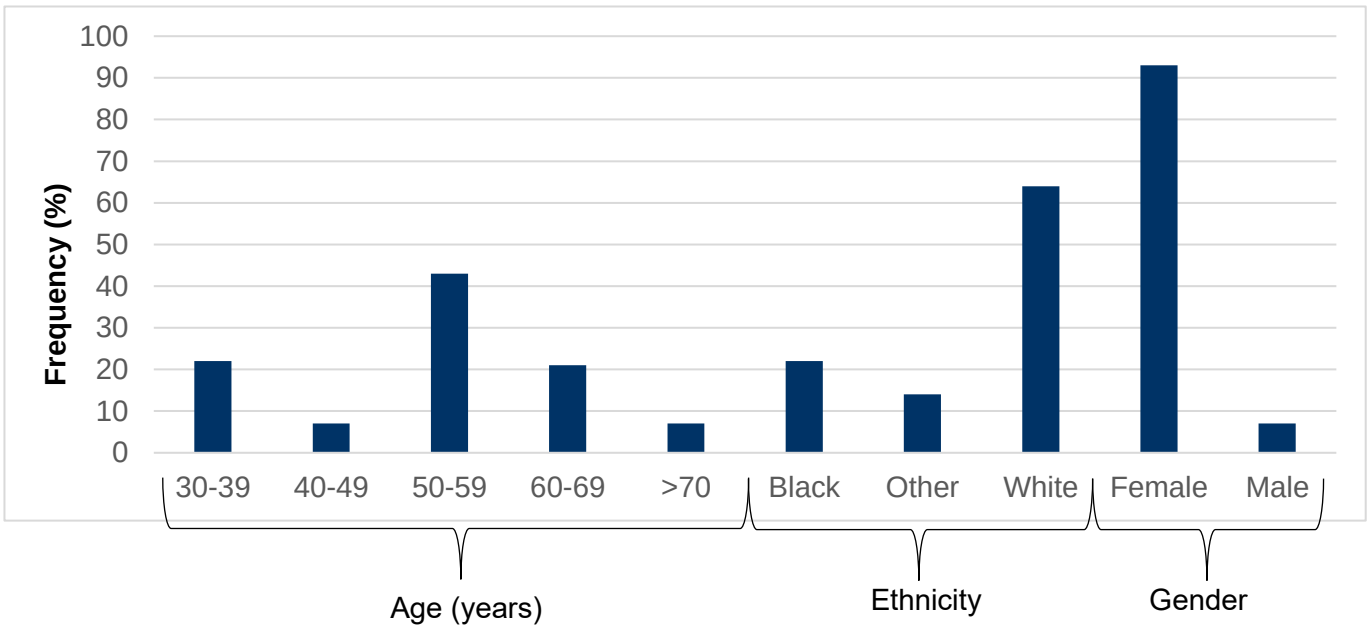

Figure 3.14: Age, ethnic and gender distribution of respiratory ADRs.

3.6.7 Digestive system adverse drug reactions reported in patient charts

The age group 50-59 years experienced most of the digestive system ADRs (e.g. nausea, vomiting, diarrhoea, reflux and constipation), as demonstrated in Figure 3.15.

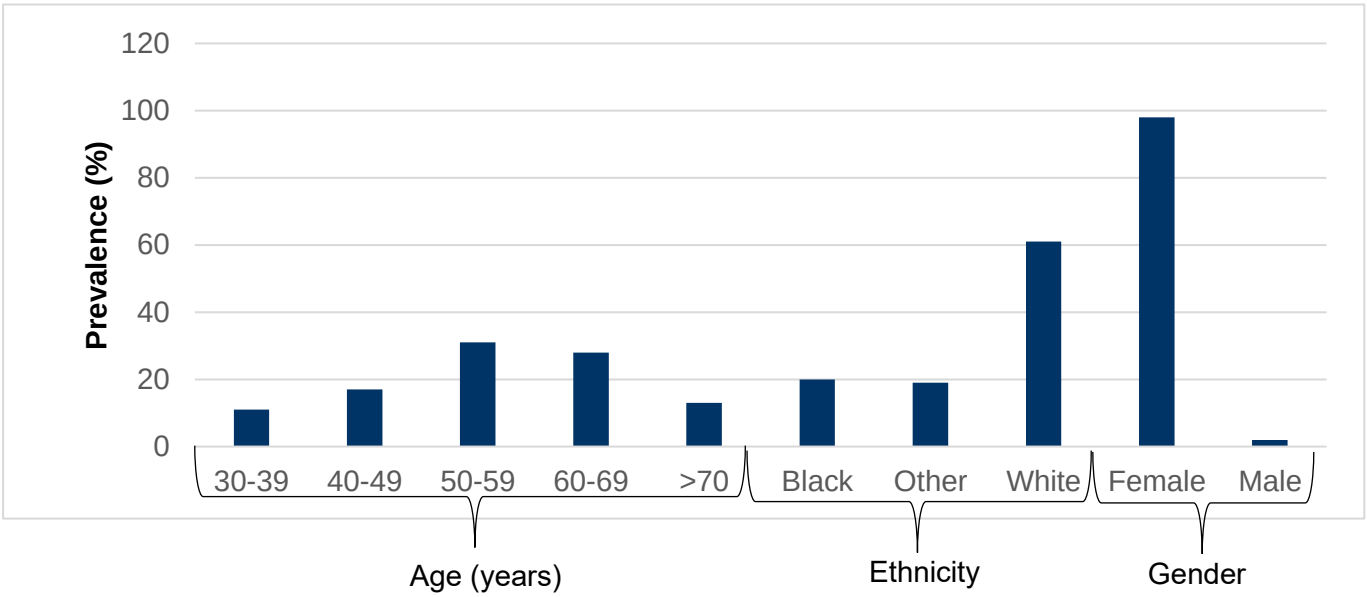

Figure 3.15: Age, ethnic and gender distribution of digestive system ADRs.

3.6.8 Urinary system adverse drug reactions reported in patient charts

The age group 60-69 years experienced most of the urinary system ADRs (e.g. decreased eGFR, burning urine, incontinence), as demonstrated in Figure 3.16.

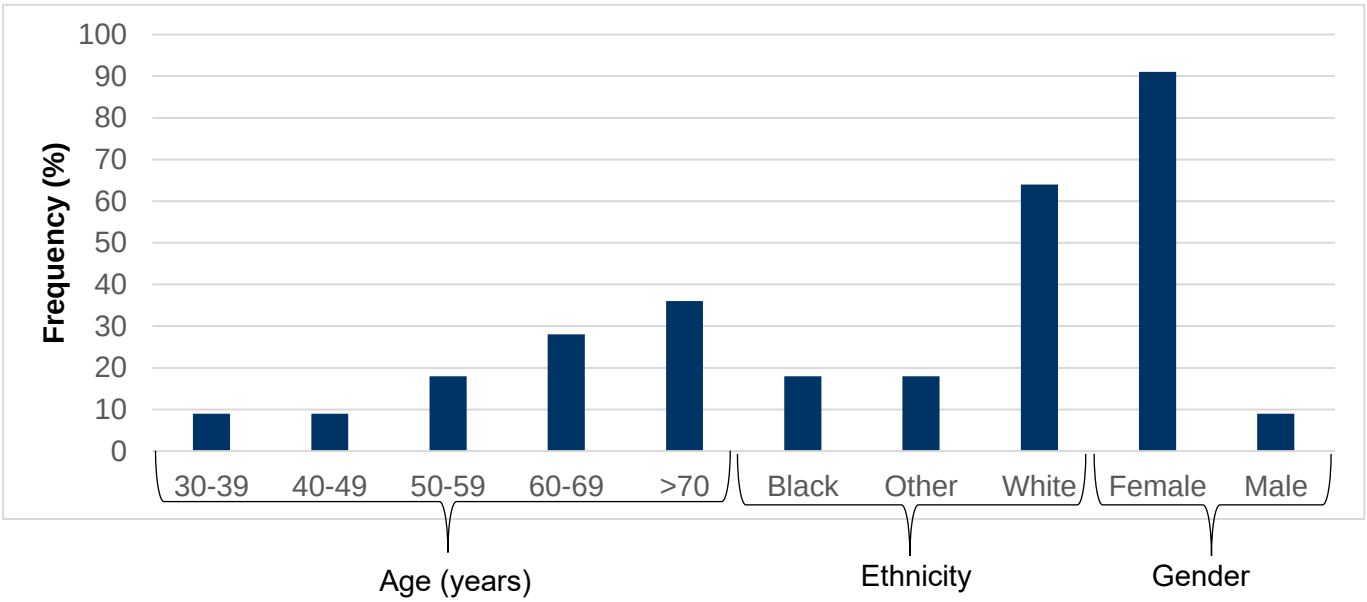

Figure 3.16: Age, ethnic and gender distribution of urinary system ADRs.

3.6.9 Reproductive system adverse drug reactions reported in patient charts

The age group 40-49 years experienced most of the reproductive system adverse effects. This included cases of amenorrhea and an ovarian cyst. The reproductive system adverse effects were evenly distributed between Black and White patients, as demonstrated in Figure 3.17.

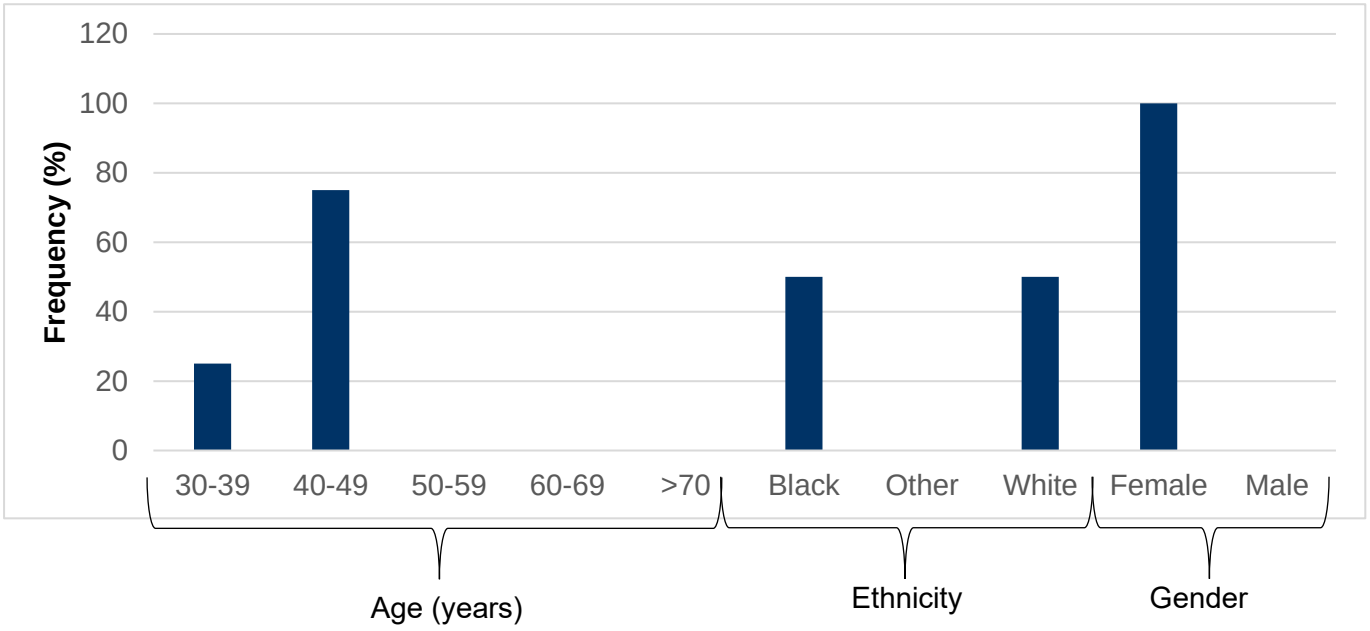

Figure 3.17: Age, ethnic and gender distribution of reproductive system ADRs.

3.6.10 Integumentary system adverse drug reactions reported in patient charts

The age group 50-59 years experienced the majority of the integumentary system ADRs (e.g. alopecia, skin rash, nail changes), as demonstrated in Figure 3.18.

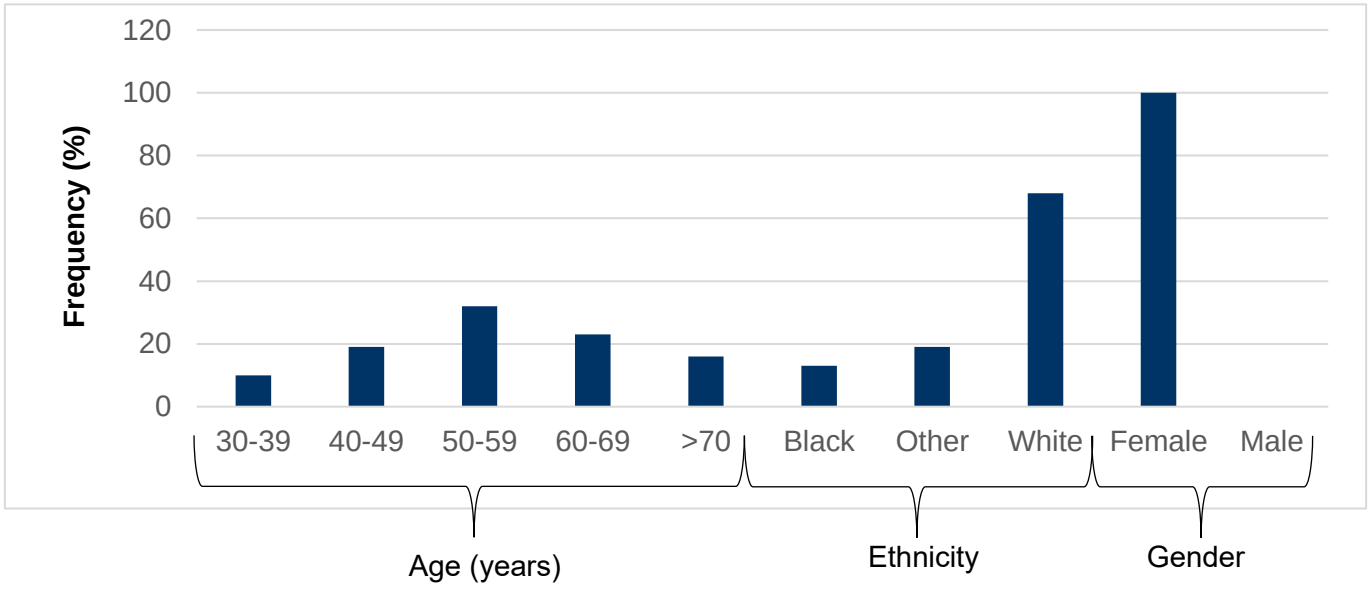

Figure 3.18: Age, ethnic and gender distribution of integumentary system ADRs.

3.6.11 Blood-related adverse drug reactions reported in patient charts

The age group 50-59 years experienced the majority of the blood related ADRs (e.g. anaemia, Leukopenia, neutropenia, lymphopenia), as demonstrated in Figure 3.19.

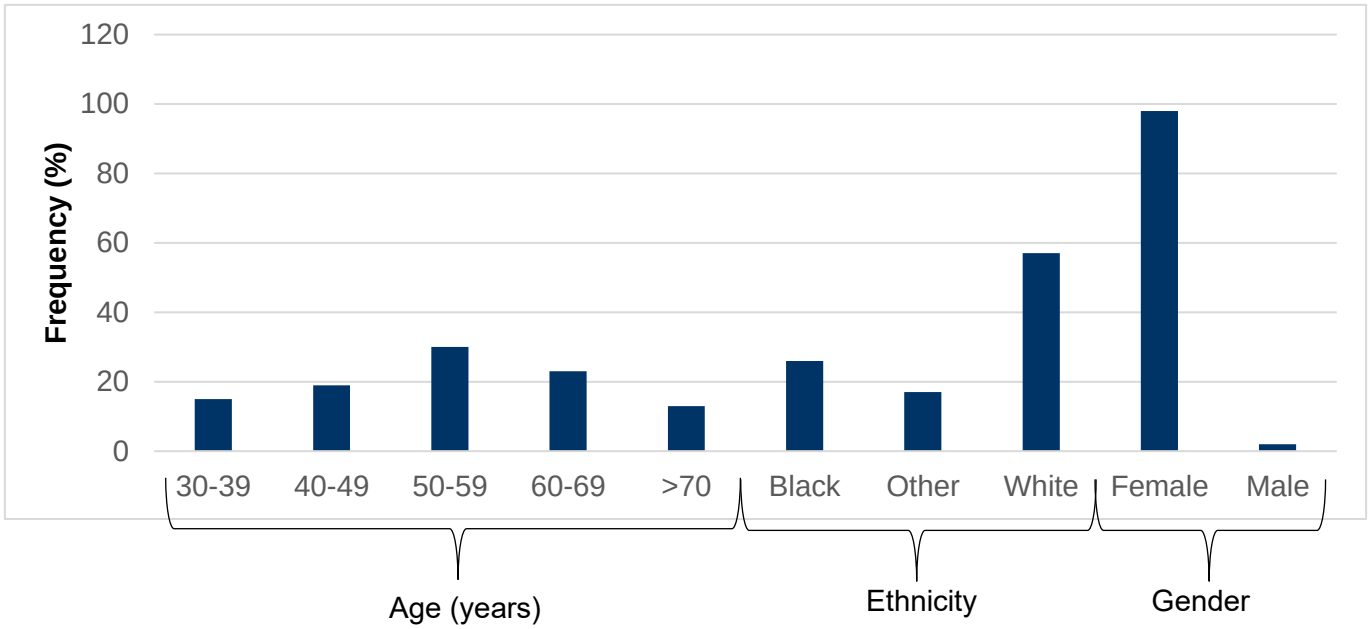

Figure 3.19: Age. ethnic and gender distribution of blood related ADRs.

3.6.12 Psychiatric adverse drug reactions reported in patient charts

The age group 50-59 years experienced the majority of the psychiatric ADRs (e.g. anxiety, emotional lability, occasional depression). A statistically significant correlation (p=0.014) was found between other comorbidities and the number of psychiatric adverse effects (Figure 3.20). This correlation can be attributed to the fact that comorbidities such as depression and bipolar depression were classified as other during the data collection process.

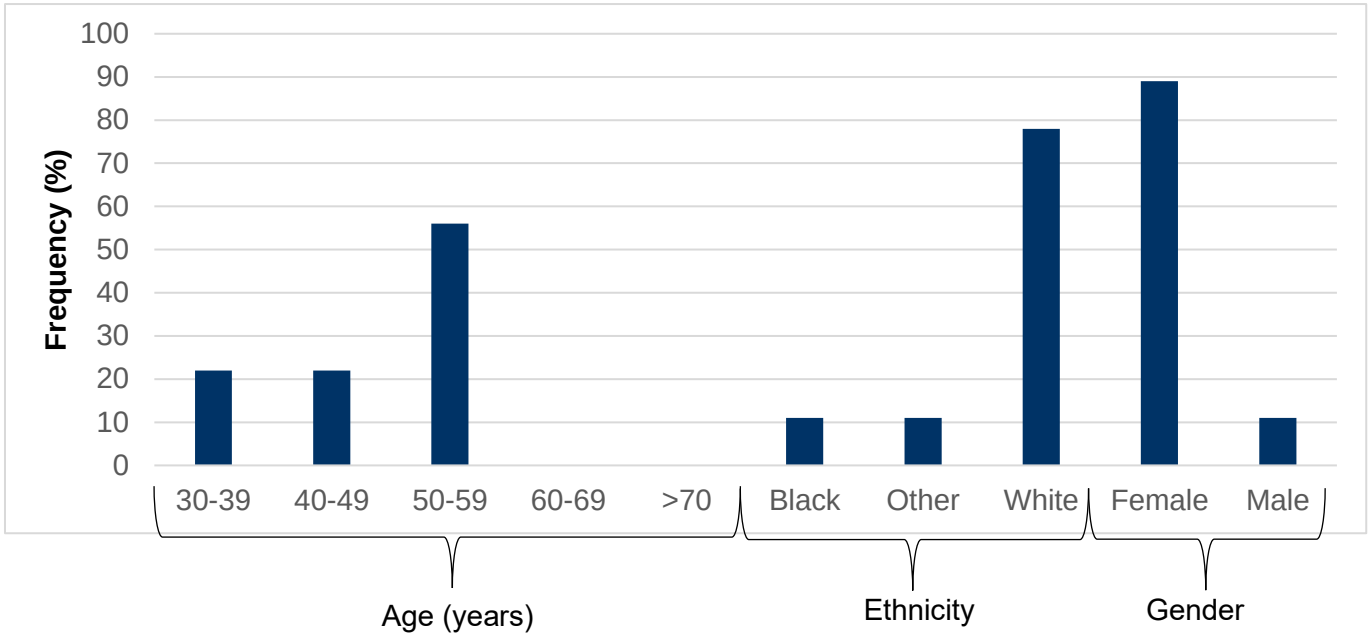

Figure 3.20: Age, ethnic and gender distribution of psychiatric ADRs.

3.6.13 Vascular adverse drug reactions reported in patient charts

The age group 50-59 years experienced the majority of the vascular ADRs (e.g. nose bleeds, hot flushes, phlebitis).

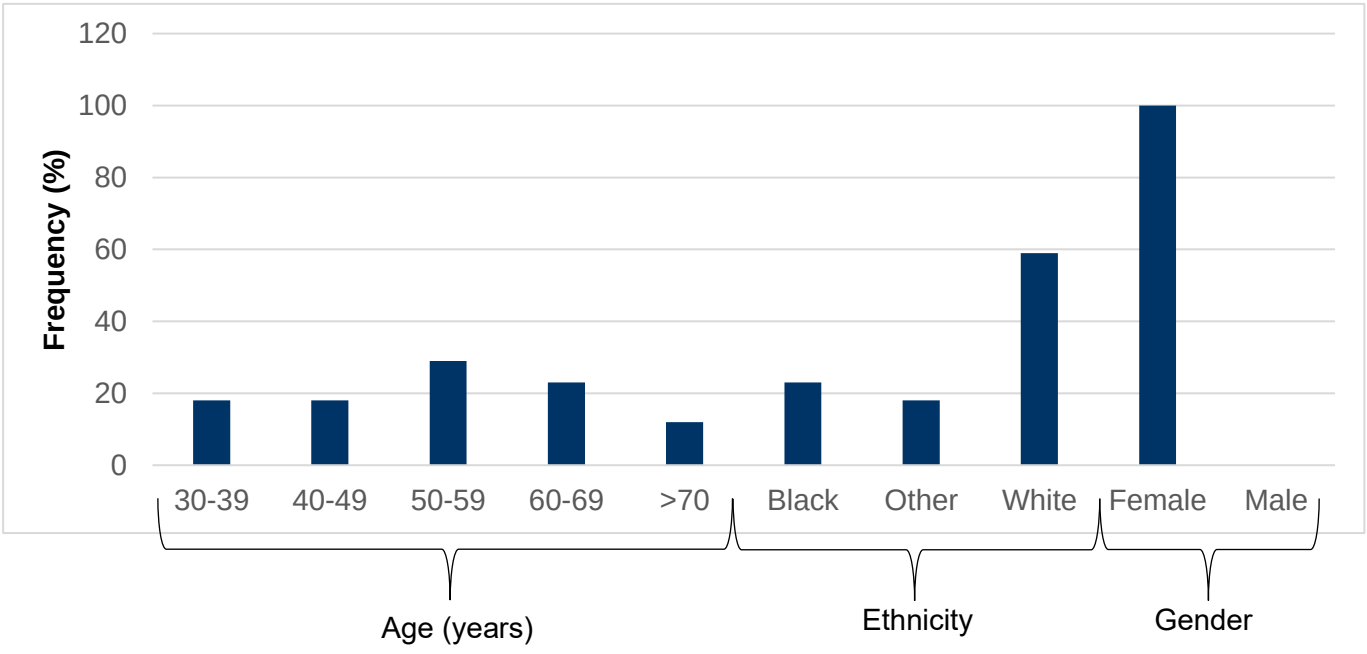

Figure 3.21: Age, ethnic and gender distribution of vascular ADRs.

3.6.14 Infections reported in patient charts

The age group 60-69 years experienced most of the infections reported in the study (e.g. flu, cold sores, nail infections, cellulitis). A statistically significant correlation (p=0.043) was found between hypertension and the number of infections related adverse effects hypertensive patients experienced.

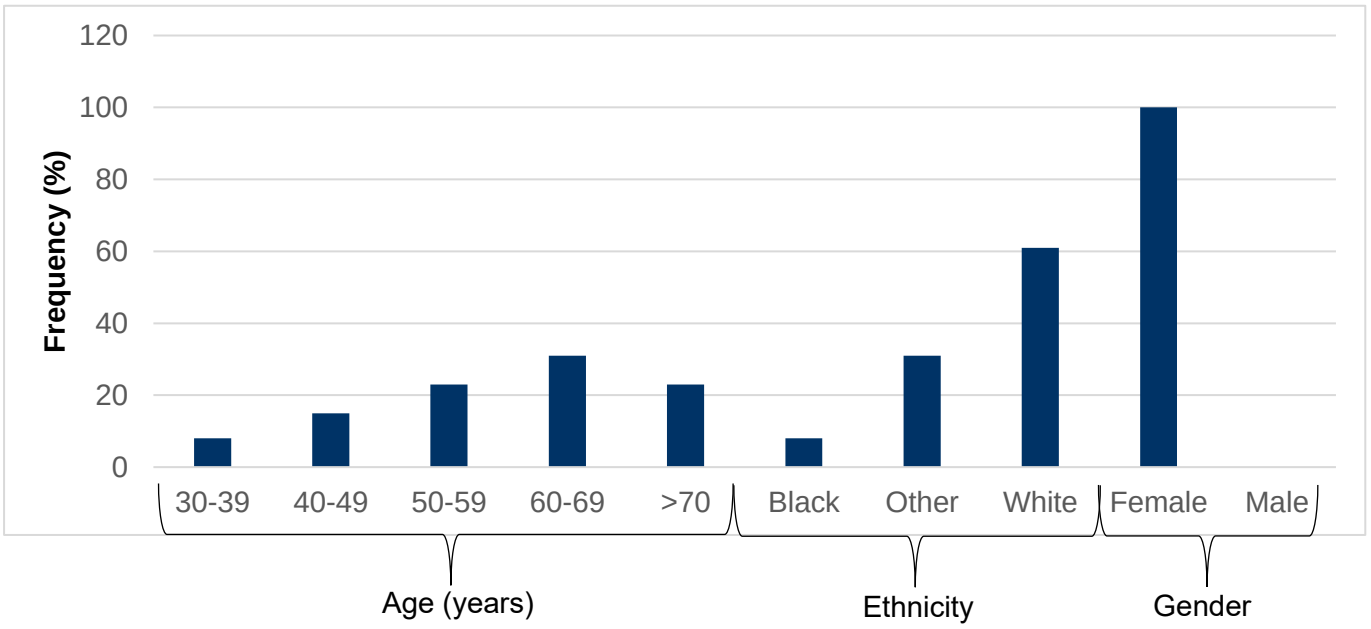

Figure 3.22: Age, ethnic and gender distribution of infection.

3.6.15 Nutrition-related adverse drug reactions reported in patient charts

The age group 60-69 years experienced the majority of the nutrition related ADRs (e.g. iron, Vit D and Vit B12 deficiency).

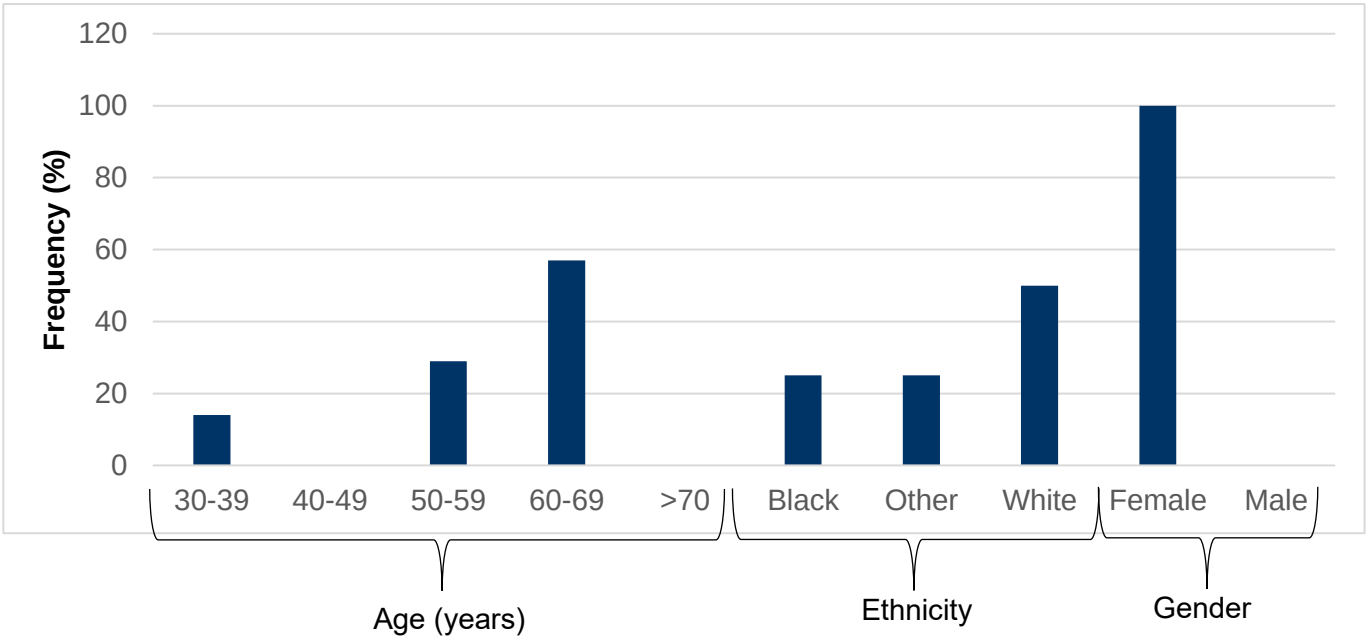

Figure 3.23: Age, ethnic and gender distribution of nutrition related ADRs.

3.6.16 Eye-related adverse drug reactions reported in patient charts

The age group 60-69 years experienced the majority of the eye related ADRs (e.g. watery eyes). These ADRs were mainly experienced by white patients.

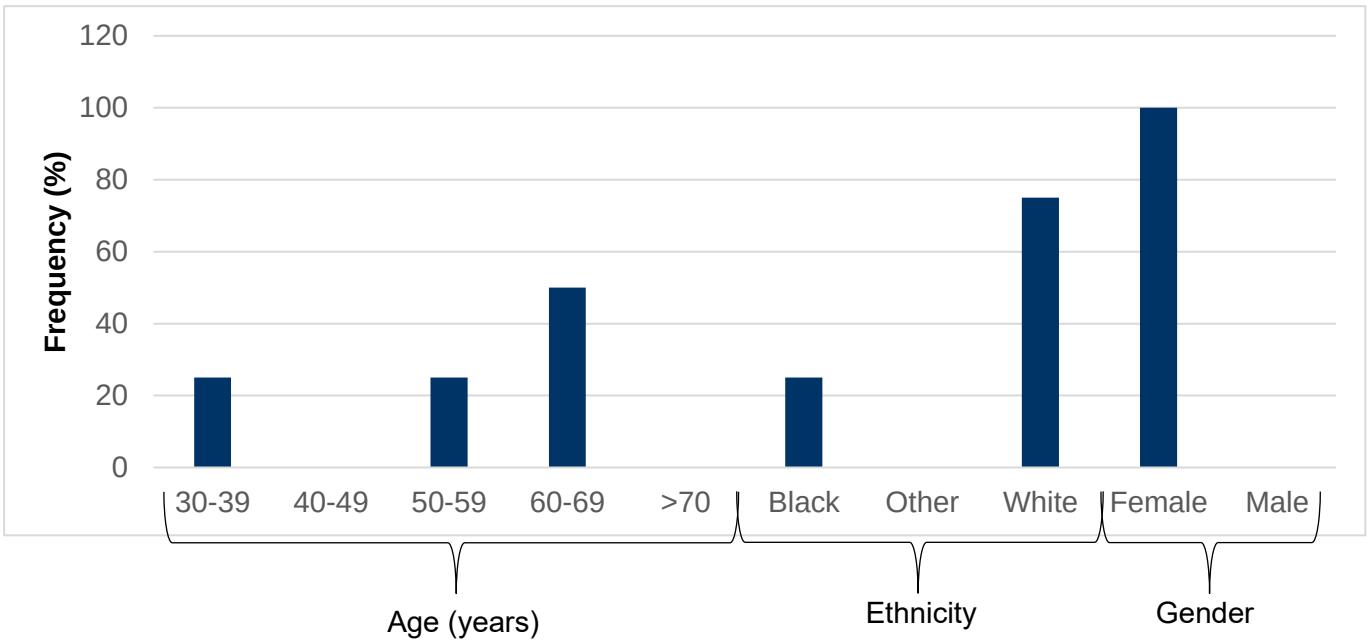

Figure 3.24: Age, ethnic and gender distribution of eye related ADRs.

3.7 Data from the WHO VigiAccess Adverse Drug Reaction database

3.7.1 Paclitaxel

There are 175,377 adverse drug reactions reported for paclitaxel on the WHO VigiAccess Adverse Drug Reaction database, with 2% of the reports from Africa. The ten most reported adverse drug reactions for paclitaxel are:

1. Blood and lymphatic system disorders (16%)
2. General disorder and administration site conditions (13%)
3. Gastrointestinal disorders (10%)
4. Respiratory, thoracic and mediastinal disorders (8%)
5. Skin and subcutaneous disorders (8%)
6. Nervous system disorders (7%)
7. Vascular disorders (6%)
8. Musculoskeletal and connective tissue disorders (5%)
9. Infections and infestations (3%)
10. Immune system disorders (3%)

"Investigations (8%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories, such as white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence.

3.7.2 Docetaxel

There are 153,853 adverse drug reactions reported for docetaxel on the WHO VigiAccess Adverse Drug Reaction database, with 1% of the reports from Africa. The ten most reported adverse drug reactions for docetaxel are:

1. Skin and subcutaneous tissue disorders (17%)
2. Blood and lymphatic system disorders (16%)
3. General disorders and administration site reactions (13%)
4. Gastrointestinal disorders (10%)
5. Respiratory, thoracic, and mediastinal disorders (6%)
6. Psychiatric disorders (5%)
7. Musculoskeletal and connective tissue disorders (4%)
8. Nervous system disorders (4%)
9. Vascular disorders (4%)

10. Infections and infestations (3%)

"Investigations (6%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories, such as white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence.

3.7.3 Doxorubicin

There are 102 902 adverse drug reactions reported for doxorubicin on the WHO VigiAccess Adverse Drug Reaction database, with 2% of the reports from Africa. The ten most reported adverse drug reactions for AC are:

1. Blood and lymphatic system disorders (17%)
2. Gastrointestinal disorders (13%)
3. General disorders and administration site reactions (13%)
4. Infections and infestations (7%)
5. Skin and subcutaneous tissue disorders (7%)
6. Nervous system disorders (5%)
7. Respiratory, thoracic, and mediastinal disorders (5%)
8. Cardiac disorders (4%)
9. Injury. poisoning and procedural complications (4%)
10. Neoplasms benign, malignant, and unspecified (including cysts and polyps) (4%)

"Investigations (6%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories, such as white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence.

3.7.4 Epirubicin

There are 29,576 adverse drug reactions reported for epirubicin on the WHO VigiAccess Adverse Drug Reaction database, with 1% of the reports from Africa. The ten most reported adverse drug reactions for epirubicin are:

1. Blood and lymphatic system disorders (31%)
2. Gastrointestinal disorder (13%)
3. General disorder and administration site conditions (10%)

4. Skin and subcutaneous disorders (6%)
5. Nervous system disorders (4%)
6. Infections and infestations (4%)
7. Cardiac disorders (3%)
8. Respiratory. thoracic and mediastinal disorders (3%)
9. Neoplasms benign, malignant, and unspecified (including cysts and polyps) (2%)
10. Metabolism and nutrition disorders (2%)

"Investigations (11%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories, such as white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence.

3.7.5 Cyclophosphamide

There are 140,120 adverse drug reactions reported for cyclophosphamide on the WHO VigiAccess Adverse Drug Reaction database, with 1% of the reports from Africa. The ten most reported adverse drug reactions for cyclophosphamide are:

1. Blood and lymphatic system disorders (20%)
2. General disorders and administration site reactions (12%)
3. Gastrointestinal disorders (11%)
4. Infections and infestations (8%)
5. Skin and subcutaneous tissue disorders (6%)
6. Nervous system disorders (5%)
7. Respiratory, thoracic, and mediastinal disorders (4%)
8. Neoplasms benign, malignant, and unspecified (including cysts and polyps) (4%)
9. Injury. poisoning and procedural complications (3%)
10. Metabolism and nutrition disorders (3%)

3.7.6 Trastuzumab

There are 49,654 adverse drug reactions reported for trastuzumab on the WHO VigiAccess Adverse Drug Reaction database, with 2% of the reports from Africa. The ten most reported adverse drug reactions for trastuzumab are:

1. General disorders and administration site conditions (18%)
2. Gastrointestinal disorders (10%)

3. Nervous system disorders (7%)
4. Skin and subcutaneous disorders (7%)
5. Cardiac disorders (6%)
6. Respiratory, thoracic, and mediastinal disorders (6%)
7. Blood and lymphatic system disorders (6%)
8. Musculoskeletal and connective tissue disorders (5%)
9. Infections and infestations (5%)
10. Injury, poisoning and procedural complications (5%)

"Investigations (8%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories, such as white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence.

3.7.7 Carboplatin

There are 120,927 adverse drug reactions reported for carboplatin on the WHO VigiAccess Adverse Drug Reaction database, with 2% of the reports from Africa. The ten most reported adverse drug reactions for carboplatin are:

1. Blood and lymphatic disorders (19%)
2. Gastrointestinal disorders (11%)
3. General disorders and administration site conditions (11%)
4. Skin and subcutaneous tissue disorders (9%)
5. Respiratory, thoracic, and mediastinal disorders (7%)
6. Nervous system disorders (6%)
7. Vascular disorders (4% 9720)
8. Infections and infestations (4%)
9. Metabolism and nutrition disorders (3%)
10. Immune system disorders (3%)

"Investigations (8%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories (white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence).

3.7.8 Pertuzumab

There are 16,182 adverse drug reactions reported for pertuzumab on the WHO VigiAccess Adverse Drug Reaction database, with 1% of the reports from Africa. The ten most reported adverse drug reactions for pertuzumab are:

1. General disorders and administration site conditions (17%)
2. Gastrointestinal disorders (14%)
3. Skin and subcutaneous tissue disorders (9%)
4. Nervous system disorders (7%)
5. Blood and lymphatic disorders (7%)
6. Infections and infestations (6%)
7. Respiratory, thoracic and mediastinal disorders (6%)
8. Injury, poisoning and procedural complications (6%)
9. Musculoskeletal and connective tissue disorders (4%)
10. Cardiac disorders (4%)

"Investigations (6%)" were omitted from the list of 10 most reported adverse drug reactions as it includes conditions covered by other categories. (white cell count decrease, haemoglobin decrease, platelet count decrease, weight decrease, body temperature increase, and pulse absence).

3.7.9 Cyclophosphamide, Methotrexate, and 5-Fluorouracil (CMF)

There are 17 adverse drug reactions reported for CMF on the WHO VigiAccess Adverse Drug Reaction database, where 0% of the reports were from Africa. The ten most reported adverse drug reactions for CMF are:

1. Gastrointestinal disorders (32%)
2. Skin and subcutaneous disorders (14%)
3. Blood and lymphatic system disorders (11%)
4. General disorders and administration site conditions (11%)
5. Neoplasms benign, malignant, and unspecified (including cysts and polyps) (11%)
6. Musculoskeletal and connective tissue disorders (7%)
7. Nervous system disorders (4%)
8. Psychiatric disorders (4%)
9. Respiratory, thoracic, and mediastinal disorders (4%)
10. Surgical and medical procedures (4%)

3.8 A comparative analysis between study findings and the WHO VigiAccess Adverse Drug Reaction database

3.8.1 Taxane-based treatment

Four patients were treated with a taxane only (one with paclitaxel and three with a combination of docetaxel and cyclophosphamide).
The adverse effects most reported at Sandton Medical Oncology Centre were nervous, digestive, integumentary and vascular. This correlates with skin and subcutaneous tissue disorders and gastrointestinal disorders being some of the most reported adverse effects on the WHO VigiAccess Adverse Drug Reaction database.

3.8.2 Combination of a taxane and Trastuzumab treatment

Three patients were treated with a taxane (paclitaxel) and trastuzumab.

The adverse effects most reported at Sandton Medical Oncology Centre were nervous. lymphatic. digestive. blood. vascular and infections. This correlates with blood lymphatic and gastrointestinal disorders most reported on the WHO VigiAccess Adverse Drug Reaction database for Paclitaxel and gastrointestinal and nervous system disorders being the most reported for Trastuzumab.

3.8.3 Combination of an anthracycline followed by a taxane treatment

Twenty-eight patients were treated with an anthracycline (doxorubicin or epirubicin) in combination with cyclophosphamide. followed by sequential treatment with a taxane [docetaxel (3) or paclitaxel (25)].

The adverse effects most reported at Sandton Medical Oncology Centre were blood. digestive. nervous and integumentary. This correlates with blood and lymphatic system disorders being the most reported on the WHO VigiAccess Adverse Drug Reaction database for doxorubicin, epirubicin, cyclophosphamide and paclitaxel. Digestive system disorder was reported for doxorubicin, epirubicin, cyclophosphamide, paclitaxel and, docetaxel. Nervous system disorders were among the most reported adverse effects of epirubicin. Skin and subcutaneous tissue disorders were reported for doxorubicin, epirubicin, cyclophosphamide, paclitaxel and docetaxel.

3.8.4 Combination of an anthracycline and Cyclophosphamide followed by a taxane and Trastuzumab treatment

Six patients were treated with an anthracycline in combination with cyclophosphamide (AC (4) or EC (2)), followed by sequential treatment with paclitaxel in combination with Trastuzumab.

The adverse effects most reported at Sandton Medical Oncology Centre were nervous, blood. digestive, and skeletal. This correlates with blood, lymphatic, and gastrointestinal disorders being the most reported on the WHO VigiAccess Adverse Drug Reaction database for doxorubicin, epirubicin, cyclophosphamide, paclitaxel, and trastuzumab. Nervous system disorders were among the most reported adverse effects on the WHO VigiAccess Adverse Drug Reaction database for epirubicin and trastuzumab.

3.8.5 Combination of a taxane, Trastuzumab and Pertuzumab treatment

One patient received a combination of paclitaxel, trastuzumab and pertuzumab. The adverse effects most reported at Sandton Medical Oncology Centre were nervous, lymphatic, digestive, integumentary and blood. This correlates with gastrointestinal skin and subcutaneous tissue disorders, which are among the most reported on the WHO VigiAccess Adverse Drug Reaction database for paclitaxel, trastuzumab, and pertuzumab. Blood and lymphatic disorders were some of the most reported adverse effects of paclitaxel and trastuzumab. Nervous system disorders were some of the most reported adverse effects of trastuzumab and pertuzumab.

3.8.6 Combination of a taxane, Trastuzumab and Pertuzumab treatment

One patient received a combination of paclitaxel, trastuzumab, and pertuzumab. The adverse effects most reported at Sandton Medical Oncology Centre were nervous, lymphatic, digestive, integumentary and blood. This correlates with gastrointestinal skin and subcutaneous tissue disorders, which are among the most reported on the WHO VigiAccess Adverse Drug Reaction database for paclitaxel, trastuzumab, and pertuzumab. Blood and lymphatic disorders were some of the most reported adverse effects of paclitaxel and trastuzumab. Nervous system disorders were some of the most reported adverse effects of trastuzumab and pertuzumab.

3.8.7 Taxotere (Docetaxel), Carboplatin and Herceptin (Trastuzumab) treatment

Five patients received TCH at Sandton Oncology. The adverse effects most reported for this regimen at the study site were blood, integumentary, digestive, nervous, and skeletal. This correlates with gastrointestinal skin and subcutaneous tissue disorders being some of the most reported adverse effects on the WHO VigiAccess Adverse Drug Reaction database for docetaxel, carboplatin, and trastuzumab. Blood and lymphatic system disorders were some of the most reported adverse effects of docetaxel and carboplatin. Trastuzumab causes the most nervous system disorders.

3.8.8 Cyclophosphamide, Methotrexate, and 5-Fluorouracil treatment

Seven patients were treated with CMF at Sandton Oncology. The adverse effects most reported at the study site were nervous, digestive, blood and integumentary. This correlates with gastrointestinal, skin and subcutaneous tissue disorders, and blood and lymphatic system disorders being the most reported on the WHO VigiAccess Adverse Drug Reaction database for CMF.

Chapter 4: Conclusion

4. Chapter overview

The following are discussed in Chapter 4: the conclusions from this study, the strengths and limitations of this study as well as recommendations.

4.1 Conclusion

Most patients included in the study were white, aged 50-59, and diagnosed with Stage II breast cancer. The majority of the patients were oestrogen and progesterone positive and HER2 negative.

The majority of patients, irrespective of ethnicity, received a combination of an anthracycline and cyclophosphamide combination followed by a taxane. Most of the patients who received this treatment were aged 30-59. Most patients >70 years, received treatment with CMF.

White patients reported the most adverse effects per physiological system except reproductive system adverse effects. White patients reported the most adverse effects because the study sample consisted of 57.4% white individuals. The number of comorbidities present in a specific patient increases with age. The most comorbidities were seen in white patients. The most common comorbidities found in the study patients were overweight, hypertension, obesity, dyslipidaemia, and diabetes. The type of comorbidities found in this study sample correlates with the findings of other studies.

The majority of the patients for which dose reductions were implemented, experienced five or more adverse effects during their treatment. More than half of the termination of treatment cases were preceded by a dose reduction.

No statistically significant correlation was found between any of the ethnic groups and the total number of adverse effects experienced. No statistically significant correlation was found between any of the age groups and the total number of adverse effects experienced. A statistically significant correlation was found between other comorbidities and the number of psychiatric adverse effects. A statistically significant correlation was found between hypertension and the number of infections related adverse effects hypertensive patients

experienced. A statistically significant correlation was found between dyslipidaemia and the number of lymphatic system adverse effects.

The chemotherapy-related adverse effects show similarity to the adverse effects reported on the World Health Organisation's VigiAccess Adverse Drug Reaction database, particularly adverse effects of the digestive, integumentary, haematological and lymphatic systems.

The ethnic composition of the study sample does not reflect the ethnic distribution observed in the country. This could be due to fact that the state of health is shaped by numerous elements, among them being disparities stemming from the historical past of apartheid and the socio-economic standing of individuals, often delineated by racial divides. In South Africa, research has indicated that a significant portion of individuals who have access to private healthcare services belong to the white ethnic group.

4.2 Study strengths

Sixteen point eight million people in low-and middle-income countries, like South Africa, will be diagnosed with cancer in 2050. In 2020, breast cancer was the most diagnosed type of malignancy in women, and South Africa may have the highest number of male patients diagnosed with breast cancer.

Studies with information on chemotherapy related ADRs in South Africa are lacking. This is also the first study of its kind done at Sandton Medical Oncology. Looking at the geographical distribution reported on the WHO VigiAccess Adverse Drug Reaction database, it is evident that very few adverse effects are reported by healthcare workers in Africa. The findings from this study can be generalized to patients receiving treatment in the private healthcare sector of South Africa.

By sharing the findings from this study with oncologists and other healthcare professionals at Sandton Medical Oncology, patients' treatment can be optimized by knowing which adverse effects are more likely to occur for a particular patient based on age, ethnicity and comorbidities. The expected adverse effects can be discussed with patients to better prepare them for what is to come once chemotherapy starts. Specific pre-medication can be prescribed to prevent the expected adverse effects.

4.3 Limitations

A limitation of this study was that data collection was done at a single institution. Sandton Oncology is in Morningside, Sandton, an affluent suburb of Johannesburg. The data may not be representative of the broader population of South Africa as the minority of patients can afford private healthcare in South Africa. The small sample size limits the generalizability of the study findings.

A retrospective study design is also a limitation because causation cannot be established as effectively as in a prospective study design.

Four oncologists practice at Sandton Medical Oncology. Each oncologist completes their follow-up notes differently. Including medical charts from all four oncologists in the study may have led to inconsistency in recording comorbidities and adverse effects.

Adverse drug reactions were rarely recorded in the medical charts in terms of the CTCAE version 5.0, and data had to be interpreted based on the number of adverse effects experienced and not the severity thereof.

A limitation of this study was that the reason for termination of chemotherapy was not recorded during the data collection process e.g. disease progression, chemotherapy related toxicities, complete response to chemotherapy, or personal decision.

The findings from this study were difficult to compare with the results from the WHO VigiAccess Adverse Drug Reaction database because adverse effects were grouped differently. For example, blood and lymphatic system disorders are group together on the VigiAccess Adverse Drug Reaction database and in this study, it was split into different categories. The VigiAccess Adverse Drug Reaction database includes a category for Investigations which includes adverse effects that was classified in this study under specific categories e.g. abnormal blood results was classified under the category for blood and an abnormal echocardiogram was classified under the category for cardiovascular adverse effects.

4.4 Recommendations

The findings from this study will be shared with the oncologists and other healthcare professionals at Sandton Medical Oncology. This will help the oncologists to take data explicitly collected from their practice into consideration when making clinical decisions about a patient’s treatment plan.

A prospective design study will strengthen the study's results focused on comorbidities and chemotherapy related ADRs.

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Appendices

Appendix 1: Data collection tool (REDCap®)

Participant information

Record ID	_____
Medical record number	_____
Age of the participant	_____
Gender	◯ Male ◯ Female ◯ Other
Ethnicity of the participant	◯ Black ◯ White ◯ Colored ◯ Indian ◯ Asian ◯ Other

Disease information

Hormone receptor status	☐ Estrogen positive ☐ Estrogen negative ☐ Progesterone positive ☐ Progesterone negative ☐ HER2 positive ☐ HER2 negative ☐ Triple negative
Stage of breast	◯ Stage 0 ◯ Stage I ◯ Stage II ◯ Stage III
Comorbidities present at time of diagnosis	☐ Hypertension ☐ High cholesterol ☐ Diabetes ☐ HIV positive ☐ Underweight (BMI < 18.5) ☐ Normal BMI (18.5-24.9) ☐ Overweight (BMI 25-29.9) ☐ Obesity (BMI>30) ☐ Other
Specify other comorbidities	_____

Treatment information

Chemotherapeutic regimen prescribed	☐ Anthracyclines ☐ Anthracycline followed by taxane ☐ Anthracycline followed by taxane and trastuzumab ☐ Taxanes ☐ Taxane-trastuzumab-pertuzumab ☐ Trastuzumab ☐ Pertuzumab ☐ TCH ☐ CMF ☐ Other
Specify the regimen prescribed	_____
Stage of treatment	◯ First round ◯ Second round ◯ Third round ◯ Other
Adjuvant treatment given with chemotherapy	☐ Radiation ☐ Surgery ☐ None
Administered as neoadjuvant treatment	☐ Yes ☐ No

Chemotherapeutic toxicity

Chemotherapeutic toxicities reported	○ Yes ○ No
Cycle at which chemotherapeutic toxicity developed	_____
Chemotherapeutic toxicity participant experienced	☐ Skeletal ☐ Muscular ☐ Nervous ☐ Endocrine ☐ Cardiovascular ☐ Lymphatic ☐ Respiratory ☐ Digestive ☐ Urinary ☐ Reproductive ☐ Integumentary ☐ Blood ☐ Psychiatric ☐ Vascular ☐ Infections ☐ Nutrition ☐ Eye
Specify the chemotherapeutic toxicity	_____
Severity of chemotherapeutic toxicity (CTCAE Grade 1/2/3/4/5/not specified)	_____

Corrective actions after chemotherapeutic toxicity

Modification to agents used in treatment	◯ Yes ◯ No
Dose reduction implemented	◯ Yes ◯ No
Treatment terminated?	◯ Yes ◯ No
Specify the corrective action implemented	_____

Appendix 2: Study protocol

CANDIDATE'S SURNAME: MINNS	FIRST NAME: CHANTELLE		STUDENT NUMBER: 2623792
CURRENT QUALIFICATIONS: BACHELOR OF PHARMACY (B.PHARM)			
TEL: N/A	CELL: 072 426 5008	E-MAIL: CHANTELLEMINNS9@GMAIL.COM	FAX: N/A
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MSc MED (PHARMACOTHERAPY)			
PART-TIME OR FULL-TIME: PART-TIME		Sex: F x M	
FIRST REGISTERED FOR THIS DEGREE: 2023	TERM: FIRST TERM	YEAR: 2023	
DEPARTMENT: DEPARTMENT OF PHARMACY AND PHARMACOLOGY			
TITLE OF PROPOSED RESEARCH: INVESTIGATING THE CORRELATION BETWEEN DEMOGRAPHIC AND COMORBIDITY PROFILES WITH CHEMOTHERAPEUTIC TOXICITY EXPERIENCES IN EARLY-STAGE BREAST CANCER PATIENTS IN A PRIVATE MEDICAL ONCOLOGY PRACTICE IN SOUTH AFRICA			
CANDIDATE'S SIGNATURE: CMinns		DATE: 22 MAY 2023	
SUPERVISOR 1: ZELNA BOOTH		SUPERVISION: 50%	
SUPERVISOR'S QUALIFICATIONS: B.PHARM; M.MPHARM; PhD CANDIDATE			
SUPERVISOR'S DEPARTMENT: PHARMACY AND PHARMACOLOGY			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: ROOM 8M18, 8TH FLOOR, UNIVERSITY OF THE WITWATERSRAND MEDICAL SCHOOL BUILDING, 7 YORK ROAD, PARKTOWN, 2193 / 011 717 2912 / ZELNA.BOOTH@WITS.AC.ZA			
SUPERVISOR 2: DR. NEELAVENI PADAYACHEE		SUPERVISION: 25%	
SUPERVISOR'S QUALIFICATIONS: B.PHARM; M.MPHARM; PhD			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: ROOM 8M14, 8TH FLOOR, UNIVERSITY OF THE WITWATERSRAND MEDICAL SCHOOL BUILDING, 7 YORK ROAD, PARKTOWN, 2193 / 011 717 2269 / NEELAVENI.PADAYACHEE@WITS.AC.ZA			
SUPERVISOR 3: RUBINA SHAIKH		SUPERVISION: 25%	
SUPERVISOR'S QUALIFICATIONS: B.PHARM; M.MPHARM; PhD CANDIDATE			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: ROOM 8M15, 8TH FLOOR, UNIVERSITY OF THE WITWATERSRAND MEDICAL SCHOOL BUILDING, 7 YORK ROAD, PARKTOWN, 2193 / 011 717 2369 / RUBINA.SHAIKH@WITS.AC.ZA			
SYNOPSIS OF RESEARCH: ***INTRODUCTION AND JUSTIFICATION OF STUDY:*** About 24 million people will be diagnosed with cancer in 2050, and approximately 16.8 million of them will reside in low- and middle-income countries. Breast cancer is the most common type of cancer diagnosed in women worldwide. A 23% of all malignancies are breast cancer and 14% of cancer deaths are attributable to breast cancer. The prevalence of chemotherapy-induced ADRs range from 60-80%. ***AIM:*** This study aims to determine the effect of demographics and comorbidities on chemotherapeutic toxicity experienced by patients with stage 0-III breast cancer. ***METHODOLOGY:*** This study is a retrospective cohort analysis of patient charts from Sandton Oncology. The patients' charts will be reviewed to determine the effect of demographics and comorbidities on the side effects experienced by patients with stage 0-III breast cancer. Dose modifications, dose reductions as well as premature discontinuation of chemotherapy due to side effects will also be reviewed. ***EXPECTED OUTCOME/S:*** The expected outcome of this study is that the effect of demographics and comorbidities on the chemotherapy-related toxicity experienced by breast cancer patients will be demonstrated. The study may result in finding data about treatment modifications, dose reductions, and discontinuation of treatment due to adverse drug reactions.			
WITS ETHICS NOT REQUIRED: Yes (No) WITS ETHICS PENDING: (Yes) No WITS ETHICS APPROVED: Yes (No) ***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**		IF ☐ SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:	
As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.			
SIGNATURE OF SUPERVISOR/S:		22 May 2023	
PROTOCOL ACCEPTED BY HEAD OF DEPARTMENT/RESEARCH COORDINATOR	SIGNATURE	22 May 2023	
SIGNATURE PG OFFICE STAFF	REGISTERED YES..... NO.....	STAMP	

INVESTIGATING THE CORRELATION BETWEEN DEMOGRAPHIC AND CO-MORBIDITY PROFILES WITH CHEMOTHERAPEUTIC TOXICITY EXPERIENCES IN EARLY-STAGE BREAST CANCER PATIENTS IN A PRIVATE MEDICAL ONCOLOGY PRACTICE IN SOUTH AFRICA

1. Introduction

Cancer is the main cause of death in several wealthy countries (Whiteman & Wilson, 2016). Cancer is also predicted to become a primary cause of morbidity and mortality in emerging countries shortly (Singh *et al.,* 2015). In 2012, 14.1 million people were diagnosed with cancer, and about 8.2 million passed away from cancer (Whiteman & Wilson, 2016). Approximately 24 million people are estimated to be diagnosed with cancer by 2050, with 16.8 million of those residing in economically developing countries (Kingham *et al.,* 2013).

Cancer care is fast becoming essential for the public health sectors in sub-Saharan African countries. The increase in occurrence of cancer among population groups have been attributed to lifestyle changes and longer life expectancies due to modern medicine. However, the case fatality risk of cancer is approximately 75% in sub- Saharan Africa, compared to 46% in high-income countries (Kingham *et al*., 2013). Poor infrastructure, scarcity of healthcare workers, advanced stage of cancer at diagnosis, use of traditional therapies, limited treatment options, and poor treatment compliance all contribute to the high mortality rate among cancer sufferers, in developing countries (Kingham *et al*., 2013).

In 2020, there were 108 168 new cancer cases diagnosed in South Africa alone (The Global Cancer Observatory, 2021), and 112 921 new cases are predicted to be diagnosed in 2023 (Singh *et al.,* 2015). According to statistics from the Global Cancer Observatory (2021), the most common types of cancer diagnosed in women in South Africa in 2020 included cancer of the breast, cervix, colorectum, lung, and endometrium. In men, cancer of the prostate, lung and colorectum were most prevalent, along with Kaposi sarcoma, and non-Hodgkin lymphoma (The Global Cancer Observatory, 2021).

The most frequently diagnosed malignancy in women globally is breast cancer. In a fact sheet published by the Cancer Association of South Africa (CANSA), it is reported that South Africa may have the highest number of male breast cancer patients in the world. Approximately 1-3% of breast cancer patients in South Africa are male (Herbst, 2021). With 23% of all malignancies presenting as breast cancer and 14% of cancer deaths attributable to breast cancer, breast cancer has become a major health threat (Singh *et al.,* 2014).

A tumor in the breast develops when normal cells change and spread rapidly. These abnormal cells can infiltrate the surrounding organs or other parts of the body; this is known as metastatic cancer. In approximately 80% of breast cancer cases, the surrounding tissue are infiltrated. In non-metastatic breast cancer (stage 0), the tumor is only present in the milk lobules (Ghai *et al*., 2021). Fibro adenoma, fibrocystic disease, melanoma, and super fat tissue damage are the main causes of death in breast cancer patients (Ghai *et al*., 2021).

Orthodox therapy for breast cancer are surgery, radiation, and chemotherapy (On *et al*., 2022). Some new developments in breast cancer treatment include immunotherapy, hormone-based therapy, and stem cell therapy (Ghai *et al*., 2021).

Drug-induced mortality is a major public health concern as some countries spend 20% of their healthcare budget to manage adverse drug reactions (Ghai *et al*., 2021). An adverse drug reaction (ADR) is harmful and unplanned and happens at doses normally used for prophylaxis, assessment, or treatment. The prevalence of chemotherapy- induced ADRs range from 60-80% (On *et al*., 2022) and recent studies estimates that ADRs are the fourth to sixth leading cause of death (Ghai *et al*., 2021). ADRs occur more frequently in geriatric and hospitalized patients (16.6%) than in the normal adult population (4.1%) (Ghai *et al*., 2021). ADRs lead to reduced quality of life and alterations in treatment plans like delays between cycles or reduction of cycles and dose (Han *et al*., 2011). ADRs include nausea and vomiting, blood and lymphatic system disorders, hand-foot syndrome, fatigue, hypersensitivity reactions, gastrointestinal adverse effects, adverse neurological effects, and myeolosuppression (On *et al*., 2022 & Han *et al*., 2011). The type of ADR depends on the type and dose of chemotherapy, number of cycles administered, history of chemotherapy-induced ADRs, comorbid disease, health status, age, and genetics (On *et al*., 2022).

The National Cancer Institute in the United States released statistics that show that 54% of all cancer patients are 65 years and older. 61 years is the mean age for breast cancer diagnosis (Stavrou *et al.*, 2012). An estimated two-thirds of patients 65 years and older suffer from one or more comorbid diseases and take an average of four prescribed medications to manage these diseases (Stavrou *et al.*, 2012).

The prevalence of cancer increases with age and chronic diseases (Parés-Badell *et al*., 2017). In addition, most cancer patients have one or more comorbid diseases which affect the timing of diagnosis by concealing the symptoms, leading to delayed consultation with a healthcare worker, which delays referral for further examination (Boakye *et al*., 2021). In addition, comorbidities affect the choice and effectiveness of treatment options (Michalopoulou *et al*.,

2021).

Cancer patients with comorbidities have a poorer prognosis than those without comorbid diseases (Boakye *et* al., 2021). Several factors may lead to a poorer prognosis due to obesity, namely, later diagnosis, delayed self-detection, more surgical and radiotherapy complications, less efficacy of hormonal treatments, under- dosing of systematic chemotherapy, and decreased health-related quality of life (James *et al*., 2015).

Increased mortality has been linked with comorbid diseases, but the presence of these comorbid diseases may have a different effect on mortality depending on the location of cancer (Parés-Badell *et al*., 2017 and Michalopoulou *et al*., 2021). One of the ways comorbidities affect cancer survival is that comorbid patients use cancer treatment less often. Comorbidities also directly cause non-cancer death (Boakye *et al*., 2021).

Comorbidity is defined as a disease present simultaneously and independently from the disease being studied (Land *et al*., 2012). According to Sreenivas on WebMD (2021), the most common comorbidities are diabetes, high blood pressure, heart disease, and respiratory disease. Curative treatments like surgery, radiotherapy, and chemotherapy may not be possible to perform or administer when comorbidity that involves organ failure, e.g., compromised respiratory, cardiac, or renal function, are present (Land *et al*., 2012).

Diabetes, obesity, and cancer regularly co-occur. A study conducted in Sweden showed that obesity increases the risk of 15 types of cancer, with Hodgkin lymphoma in men having the highest standardized incidence ratio of 3.3. After a meta-analysis of 221 datasets, it was ascertained that the risk for common and rare malignancies increases with every 5kg/m^2 increase in body mass index (BMI). Obesity poses a high risk for vascular complications and early mortality in patients with diabetes. Oxidative stress, inflammation, and endothelial dysfunction cause organ damage in obese and hyperglycaemic patients (Mao *et al*., 2021).

On the other hand, patients with comorbid diseases visit healthcare workers frequently, which may result in increased chances of screening for cancer, leading to early detection and diagnosis (Boakye *et al*., 2021).

More than 90% of patients aged 70 years and older have some comorbidity. Furthermore, 40% of these comorbidities are classified as severe (Kim *et al.*, 2019). Elderly patients often have a lower physiologic reserve, suffer from comorbidities, use several chronic medications,

are functionally dependent on a caregiver, have inadequate social support (Kim *et al*., 2019), and experience higher hospitalization rates and adverse drug reactions from cancer treatment (McCleary *et al*., 2022).

Survival rates in African American women with breast cancer are lower than in their Caucasian counterparts. The Henry Ford Health System as well as the SEER database recognise the higher mortality rates observed in African American women (Han *et al*., 2011). A Hawaiian study found higher survival rates in Asian women than non-Hispanic white women. On the other hand, the Asian women presented with less severe breast cancer (Han *et al*., 2011).

A retrospective study comparing acute toxicity after administration of adjuvant doxorubicin-based chemotherapy between Asian and Caucasian women, found the following: grade 3 neutropenia occurred in 52% of Asian women versus 3.4% in Caucasian women. Grade 4 neutropenia occurred in 25% of Asian women versus 0.3% Caucasian women (Han *et al*., 2011).

Treatment of nonmetastatic breast cancer regularly involve anthracycline-based treatment plans. The combination of chemotherapy and a dose dense regimen is more effective in the treatment of breast cancer than traditional treatment plans, but results in higher levels of toxicity. According to the National Cancer Institute (2022), dose dense chemotherapy treatment plans involve less time between cycles than in conventional treatment plans (Han *et al*., 2011).

1.1 Problem statement

Clinical findings have indicated that chemotherapy toxicity varies in accordance with patient specific demographics and that many patients requiring chemotherapy often present with comorbidities such as diabetes, hypertension, and obesity due to lifestyle habits.

1.2 Purpose of study

The influence of patient demographics and comorbidities on chemotherapeutic toxicity are prevalent in scientific studies in countries other than South Africa. This study intends to address the gap in scientific information in the South African population and more specifically medical practice / site specific information to ensure optimal patient centred individualised care.

2. Aim and objectives

This study aims to determine a correlation between demographic profiles and the presence of pre-existing comorbidities on the chemotherapy-related side-effects experienced by patients with stage 0-III breast cancer at a large oncology center in Gauteng.

Study objectives:

a. To investigate whether specific side-effects frequently present in patients receiving chemotherapy for stage 0-III breast cancer in a particular ethnic or age group.
b. To investigate an association between specific side-effects and specific pre- existing comorbidities in patients receiving chemotherapy for stage 0-III breast cancer.
c. To investigate practices employed to attend to experienced side effects of chemotherapeutic therapy amongst patients with stage 0-III breast cancer (dose modifications, dose reductions, or premature discontinuation of chemotherapy).
d. To undertake a comparative analysis between study findings and the World Health Organizations' (WHO) VigiAccess Adverse Drug Reaction database on chemotherapeutic toxicities.

3. Methods

3.1 Study design

This study is a retrospective (January 2018 to December 2019), descriptive cohort analysis of patient medical records at Sandton Medical Oncology. Approximately 432 patients are treated at the center each year. The Sandton Oncology Centre offers a variety of services to their patients including medical oncology, radiation therapy, psychosocial care, rehabilitation facilities and sub-acute wards. Types of cancer mostly treated at Sandton Medical Oncology include breast, ovarian, non-small cell lung cancer, colorectal and urothelial.

3.2 Study site

The study site is Sandton Medical Oncology. It is a private medical oncology practice located in Sandton, Johannesburg. The practice has four practicing medical oncologists. The research worked at Sandton Medical Oncology as an oncology pharmacist during 2022 and has a working relationship with the medical oncologists.

3.3 Study participants

3.3.1 Inclusion criteria

Patient files will be included if the patient had been:

- diagnosed with stage 0, I, II, and III breast cancer from January 2018 to December 2019;
- undergoing chemotherapy;
- Age >18 years;
- Male and female patients.

3.3.2 Exclusion criteria

Incomplete patient records will be excluded from the study.

3.4 Sampling method

Approximately 432 patients are treated at Sandton Medical Oncology each year. 14.3% of South Africans (both sexes, all ages) were diagnosed with breast cancer in 2020 (The Global Cancer Observatory, 2021). Based on these statistics, about 62 patients are diagnosed with breast cancer each year. A sample size of 54 participants was calculated, using the Raosoft online sample size calculator (Raosoft, 2004).

$$N=\frac{z^2 p\,(1-p)}{d^2}$$

Equation 1: Sample size formula. *N* = sample population size; *z* = statistical level of confidence (95%); *p* = expected proportion of sample with particular characteristics (p=0.5); *d*

= margin of error (*d* = 0.05*).*

3.5 Data collection tool

Data will be collected from patient medical records at the study site, in accordance with ethical guidelines and ensuring POPIA adhered to at all times. Patient charts to be included in the study will be allocated a file number for researcher identification purposes only. No direct patient identifiers will need to be recorded at any point in time. Data collected will be captured in using the online software, REDCap®. The data collection tool (Appendix A) will be transcribed into REDCap® for ease of data collection. Data to be recorded has been outlined in the data collection sheet (Appendix A) and pertains to the main demographics of patients meeting the inclusion criteria, comorbidities, hormone receptor status (HER2, estrogen, progesterone), chemotherapy regimen prescribed, and side effects according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, after which the resultant recourse applied by the oncologist will be recorded. The objective is to investigate whether specific patient demographics and their presenting comorbidities has any effect on the side effects experienced during chemotherapy. For recorded chemotherapeutic toxicities in patient files, the researcher is to document the side effects, along with specific patient demographics and comorbidities experienced by the patient. This data will allow the researcher to evaluate whether there are correlations in patterns of certain demographics or comorbidities that are strongly linked to the different side effects experienced as a result of chemotherapeutic toxicity.

3.6 Study procedure

Ethics approval will be applied for at the University of the Witwatersrand Medical Human Research Ethics Committee (HREC). Permission to collect data at Sandton Oncology will be sought from the directors of Sandton Medical Oncology (Appendix B and C). Once permissions and ethical clearance has been received, patient charts will be reviewed in accordance with sampling method and inclusion criteria parameters. Patient charts will be accessed from the archives room at Sandton Oncology and will be manually retrieved, and each file will be reviewed on-site. The data collection tool (Appendix A) will be completed comprehensively per file, using REDCap® software. The extracted patient information will be kept confidential, with file codes assigned to data collected. Once the sample size has been reached, the data will be transferred for review, cleaning and analysis in Microsoft Excel. The data includes age and self- assigned race. Data will be stored on the researcher's personal laptop and shared with supervisors. All devices used will be password protected and the REDCap® registration and sign in details will be kept confidential by the researcher. No paper-based records or data will

be taken off the study site.

3.7 Data analysis

Data analysis will be completed using Microsoft Excel. Descriptive analyses of the patient demographic characteristics in relation to side effect profiles experienced will be determined through pivot tables and recorded as percentages and frequencies. Furthermore, comorbidity prevalence will be analysed in patients experiencing chemotherapeutic side effects. The most frequent responsive techniques employed by the treating oncologists at the study site, to assist with side effect profiles will also be determined. Chemotherapeutic toxicity reported by the study site will be compared with adverse drug reactions documented in VigiAccess for each chemotherapy regimen. Data collected at Sandton Oncology will be compared with the following data in VigiAccess as percentages: type of reported potential side effect, patient sex distribution, and age group distribution.

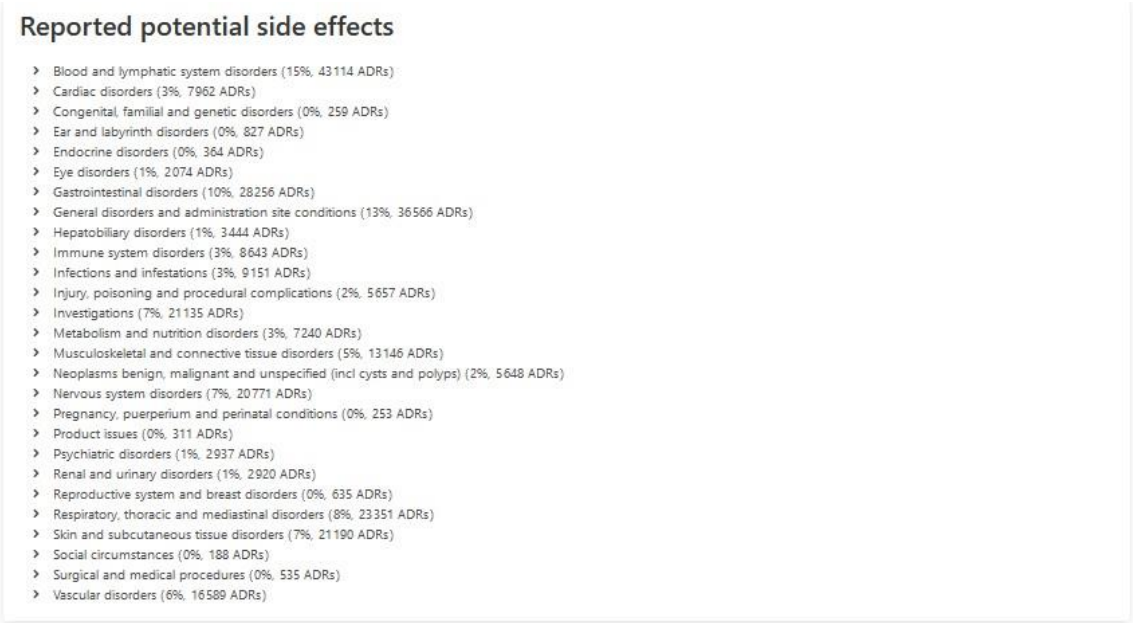

Figure 1: Side effect categories as reported in Vigiaccess for Paclitaxel

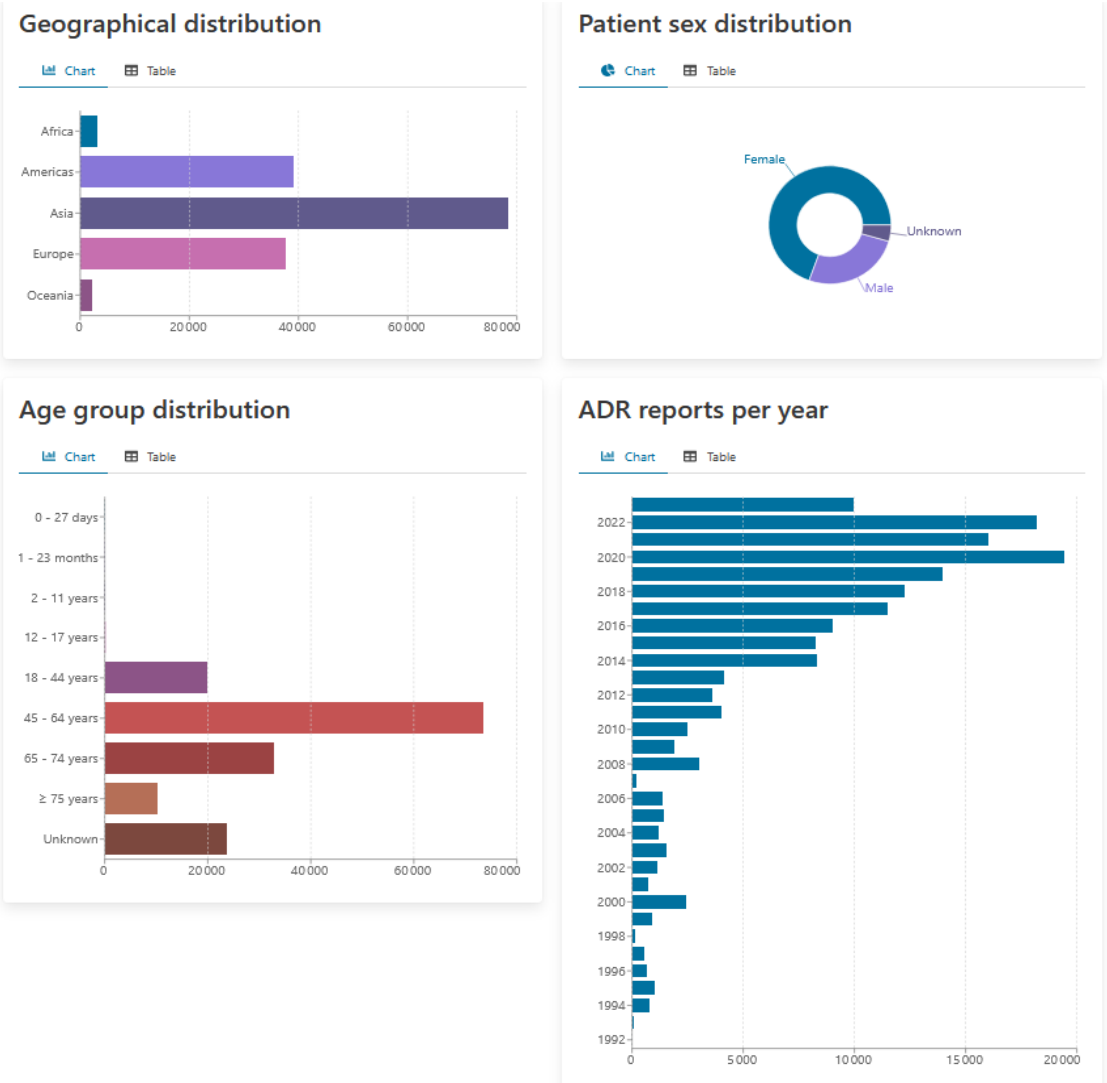

Figure 2: Data analysis of side effects reported for Paclitaxel in Vigiaccess

3.8 Ethics

An ethics application will be submitted to the University of the Witwatersrand Medical HREC. Permission for data collection will be obtained from the directors of Sandton Medical Oncology. This study entails the retrospective analysis of patient charts; therefore, no patient permission is needed. All the information that is collected in the study from patient charts will be kept confidential and will remain on site at the Sandton Oncology Centre. The study will commence once ethics approval has been obtained.

4. Timeline

2023	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol write up												
Protocol submission												

Ethics application and submission												
Literature review Writing												
Data collection												
Data analysis												
Final write-up and presentation												

5. Funding

This study will be self-funded by the researcher. Supervisor grant funding will also be available to assist in covering expenses.

6. Budget

Description	**Cost**
Internet access when on site	R 500.00
Fuel (R4.18/km AA rates)	R 2000.00
Total	**R 2500.00**

7. Dissemination and translation

The researcher will share findings from the study with the oncologists and other healthcare professionals at the study site. The researcher will aim to publish research findings in a reputable local journal.

The findings from this study will provide useful information for consideration for future oncology treatment initiations in particular population groups, should any patterns between side effect profiles be found in relation to demographics or the presence of particular comorbidities of patients requiring chemotherapy for early-stage breast cancer. During the review of articles for the literature review, most literature on this research topic compared African Americans to other ethnic groups, however, studies in South Africa are lacking. The population in South Africa is also aging as the use of modern medicine has increased life expectancies, particularly among the HIV/AIDS affected population. Healthcare professionals in South Africa tend to a large diverse population of patients and hence need to be extremely aware of including evidence-based medicine in their practice to ensure the patient-centered care model is applied and treatment is tailored to specific patient needs. This study will assist in providing information relevant to attending to this need in the field of chemotherapy.

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Appendix A: Data collection tool

File Code Allocation:	**Date:**
Age:	
Gender: Female/Male/Other	
Ethnicity: Black/White/Coloured/Indian/Asian/Other	
Hormone receptor status: Oestrogen positive or negative/Progesterone positive or negative/HER2 positive or negative/Triple negative	
Co-morbidities present:	
Chemotherapeutic regimen prescribed: Anthracyclines/Taxanes/Trastuzumab/ Pertuzumab/*CMF/Other	
Stage of breast cancer: 0/I/II/III	
Stage of treatment: First round/Second round/Third round etc.	
Side effect reported: Yes/No	
Side effect profile currently experienced: Skeletal, muscular, nervous, endocrine, cardiovascular, lymphatic, respiratory, digestive, urinary, reproductive, specify.	
Severity of side effects: CTCAE classification Grade 1/2/3/4/5	
Cycle of treatment at which side effects developed:	
Modifications to treatment agents used:	
Dose reduction implementation:	
Treatment terminated:	
Adjuvant treatment: Surgery/Radiation/None	
Neoadjuvant treatment: Yes/No	

*Combination of cyclophosphamide, methotrexate and fluorouracil

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

26 June 2023
Person No: 2623792
PAG

Ms C Minns
8 Suntorini
1 East street
Halfway Gardens Ext 4
1685
South Africa

Dear Ms Chantelle Minns

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Investigating the correlation between demographic and co-morbidity profiles with chemotherapeutic toxicity experiences in early-stage breast cancer patients in a private medical oncology practice in South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3: Ethics clearance for the study

M230631 MED23-05-022

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Chantelle Minns

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230631 MED23-05-022

NAME: (Principal Investigator)	Miss Chantelle Minns
DEPARTMENT:	Pharmacy and Pharmacology Sandton Medical Oncology, Morningside, South Africa
PROJECT TITLE:	Investigating the correlation between demographic and comorbidity profiles with chemotherapeutic toxicity experiences in early-stage breast cancer patients in a private medical oncology practice in South Africa
DATE CONSIDERED:	30/06/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Mrs Z Booth, Dr N Padayachee and Mrs R Shaikh
APPROVED BY:	Prof P Ruff, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/08/2023 **EXPIRY DATE:** 23/08/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in January each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Email signed copy of this ethics clearance certificate prior to commencing with the study hrec-medical.researchoffice@wits.ac.za

Principal Investigator Signature

09 Oct 2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Zertifikat
Certificat
Certificado
Certificate

TRREE

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

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Chantelle Minns

a complété avec succès - has successfully completed

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Release Date: 2023/05/28
CID : 4hBmym/W9T4

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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Appendix 4: Approval from the study site for data collection

SANDTON ONCOLOGY

200 Rivonia Road
Morningside, 2196
Johannesburg
South Africa

Patient-Focused Care | Tel: +27 11 883 0800 | www.sandtononcology.co.za

26 April 2023

Ethics Committee
University of the Witwatersrand
1 Jan Smuts Avenue, Braamfontein
Gauteng, 2001

RETROSPECTIVE STUDY AT SANDTON ONCOLOGY

I, the undersigned, hereby authorise Ms Chantelle Minns (student number: 2623792) to perform her study entitled: **IMPACT OF DEMOGRAPHIC PROFILE AND CO-MORBIDITIES ON CHEMOTHERAPEUTIC TOXICITY IN EARLY-STAGE BREAST CANCER PATIENTS** at Sandton Oncology.

She has the permission to collect data retrospectively from Sandton Oncology patient records.

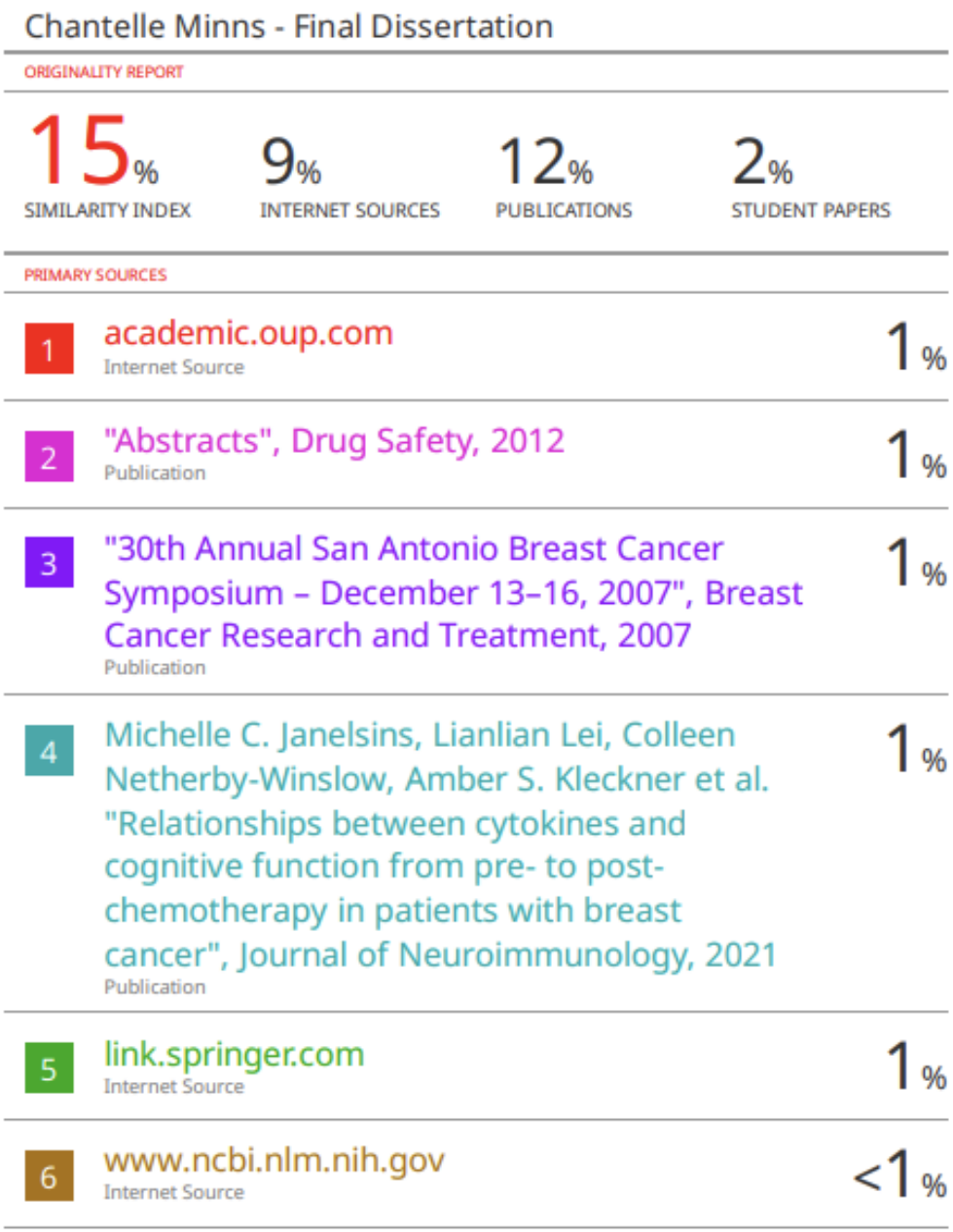
Dr Sze Wai Chan (Director)

26 APR 2023
Date

DR SZE WAI CHAN
MBBCh (Wits), MMed (Med) Wits, FCP (SA),
Cert. Medical Oncology (SA) Phys.
Specialist Physician / Medical Oncologist
HPCSA Number : MP0557811
Practice Number : 0484511

SANDTON ONCOLOGY
MEDICAL GROUP
200 RIVONIA RD
MORNINGSIDE, JHB

Appendix 5: Turnitin Plagiarism Report



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