PREVALENCE OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY AND ASSOCIATED FACTORS AMONG PATIENTS WITH BREAST CANCER ATTENDING OCEAN ROAD CANCER INSTITUTE IN TANZANIA

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By

Phiona Awuor Adagi

A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical Oncology) of

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CERTIFICATION

The undersigned certifies that she has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled; **"Prevalence of Anthracycline Induced Cardiotoxicity and Associated Factors among Patients with Breast Cancer attending Ocean Road Cancer Institute in Tanzania",** in (partial) fulfillment of the requirements for the degree of Master of Medicine (Clinical Oncology) of the Muhimbili University of Health and Allied Sciences.

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Dr. Nazima Dharsee

(Supervisor)

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Date

DECLARATION AND COPYRIGHT

I, **Phiona Awuor Adagi,** declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…… **Date**……

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DEDICATION

This dissertation is dedicated to the loving memory of my beloved mum who passed on with breast cancer. Although she was my inspiration to pursue an MMED in Clinical Oncology, unfortunately, she will not be around to see me graduate. Thank you, mum, I am because of you.

To my son “JUJU” You have made me stronger, better, and more fulfilled than I could have ever imagined. I love you to the moon and back.

To my sister Elizabeth, I would not have done this without you, the huge. the step you took for me. I am forever grateful.

ABSTRACT

Background: Anthracycline chemotherapy is the cornerstone of breast cancer treatment. Anthracyclines possess potent anti-tumor properties, and their benefits are confirmed by a considerable body of evidence. Their efficacy is undermined by dose-dependent cardiotoxicity that mandates close monitoring of cardiac function. However, there is a paucity of data regarding the prevalence of anthracycline-induced cardiotoxicity and associated factors among patients with breast cancer.

Study Objective: This study aimed to determine the prevalence of Anthracycline induced cardiotoxicity (AIC) and associated factors among patients with breast cancer undergoing treatment with anthracycline-containing regimens at ORCI.

Methodology: A cross-sectional study was conducted at ORCI among patients with histologically confirmed breast cancer on their last cycle of anthracycline chemotherapy-based regimen from Dec 2020 through June 2021. A convenience sampling technique was used. To assess anthracycline-induced cardiotoxicity, a 2D Echocardiogram was used as the main assessment tool, breast cancer patients who were on their last cycle of anthracycline were recruited as per eligibility criteria and their demographic and clinical characteristics were noted down on a prepared questionnaire. Data analysis was done using SPSS version 23 IBM. Categorical variables were summarized using frequencies while measures of central location and dispersion were used to summarize continuous variables. Logistic regression was conducted to determine factors associated with AIC. Factors with a p-value of less than 0.05 during bivariate analysis were included in the multivariate analysis. Factors with a p-value less than (0.05) were considered significant.

Results: A total of 118 breast cancer patients on anthracycline-based regimens from December 2020 through June 2021 at Ocean Road Cancer Institute were enrolled in the study. The median age of study participants was 51.5 years. 99% (117) were females. Of the enrolled participants, 9.3% (11) were confirmed to have AIC through ECHO. Nearly all 96% (113) received an AC regimen; the mean cumulative anthracycline dose was 397mg/m2 (SD 43.5). Fourteen percent (16) of the patients had a body mass index > 25; 3.4% (4) of the patients had cardiac symptoms. Upon multivariable analysis, a body mass

index greater than 25 (aOR=6.09 95% CI 1.17-31.81) was associated with an increased risk of developing AIC. Cumulative anthracycline dose ≤350 (aOR=0.08; 95% CI 0.03-0.19) and not having cardiac symptoms (aOR=0.01; 95% CI 0.01-0.19) were protective factors from AIC.

Conclusion: This study demonstrated a prevalence of anthracycline-induced cardiotoxicity and associated factors among patients with breast cancer to be 9.3% within three months of completion of an anthracycline-based chemotherapy regimen. This data is similar to other studies done internationally. It also showed that the presence of cardiac symptoms, high BMI, and low cumulative anthracycline dose had an association with AIC.

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ABBREVIATIONS

AC	Adriamycin/cyclophosphamide
AIC	Anthracycline Induced Cardiotoxicity
CHF	Congestive Heart Failure
ECHO	Echocardiogram
EPI	Epirubicin
HIC	High Income Countries
IBM	International Business Management
LMIC	Low-Middle Income Countries
LVEF	Left Ventricular Ejection Fraction
MNH	Muhimbili National Hospital
MRI	Magnetic Resonance Imaging
MUHAS	Muhimbili University of Health and Allied
ORCI	Ocean Road Cancer Institute
PI	Principal Investigator
SPSS	Statistical Package in Social Science
TAC	Taxane/ Adriamycin/Cyclophosphamide

DEFINITION OF KEY TERMS

Breast cancer: A malignant disease of the breast tissue that may involve the ducts, lobules, or connective tissue, characterized by fast-growing cells unresponsive to normal growth regulation**.**

Anthracycline: A member of a family of chemotherapy drugs that are also antibiotics. They act to prevent cell division by disrupting the structure of the DNA and terminate its function. They intercalate into the base pairs in the DNA minor grooves, and cause free radical damage of the ribose in the DNA.

Anthracycline-induced Cardiotoxicity: Anthracycline-induced cardiotoxicity (ACT) is a severe adverse drug reaction for a subset of patients treated with anthracyclines as part of chemotherapy protocols.

Congestive heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.

Prevalence is the proportion of a population with a disease or a particular condition at a specific point in time (point prevalence) or over a specified period (period prevalence).

Predictors are variables that can be used to predict some other variable or outcome.

Comorbidity- Presence of one or more additional conditions co-occurring with a primary condition e.g., Diabetes, Hypertension, HIV

Cyclophosphamide. Is a medication used as chemotherapy and to suppress the immune system used to treat breast cancer?

Taxanes– a class of antineoplastic drugs and include paclitaxel and docetaxel.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background Information

Breast cancer remains to be a significant burden on public health among women across the world despite continuous development and upgrading in screening and capability to identify disease at an early stage (1). In 2018 the world age-standardized rates of new breast cancer in females were ≥80.3/100,000 in the United States and western countries, 59.7-80.2/100,000 in South America, 38.7-46.7/100,000 in North Africa, Mexico, and Latino America as well as 46.8-59.6/100,000 in Russia, South, and North Africa and ≤ 25.6/100,000 in Sub-Saharan Africa and Asia (2).

Treatment of breast cancer ranges from surgeries, chemotherapy, and radiotherapy, and molecular as well as target therapy. Anthracycline family of drugs forms the bulk of the chemotherapy agent used in the treatment of breast cancer which has evolved since the 1950s (3). The development of this family of drugs began with daunorubicin then followed by Adriamycin (doxorubicin) which both were found effective antitumors (4–6) since then anthracyclines have been an integral part of the treatment of hematological and solid tumors example breast.

Despite enhancement in survival as a result of the introduction of anthracyclines (7,8), its use in the clinical setting is limited due to adverse events including cardiotoxicity (9). Cardiotoxicity may be acute, early, or late, with the former being reversible, affecting < 1% and manifesting as supraventricular arrhythmias, temporary electrocardiogram changes, or transient left ventricular (LV) dysfunction. The latter forms, irreversible and typified by anthracyclines (4, 5), occur at ≤ 1 year (early) and > 1 year (late) (10). A retrospective study conducted among more than 4000 patients receiving doxorubicin by Von Hoff and colleagues, 2.2% of the patients developed clinical signs and symptoms of congestive heart failure (10). However, one of the weaknesses of this study was that it was based on the sign and symptoms of congestive heart failure and reduction in LVEF without obvious symptoms.

The Von Hoff and colleagues study showed that cumulative dose was a paramount determinant of patients developing heart failure citing cumulative dose of doxorubicin, with a sharp increase in the prevalence of heart failure occurring at a cumulative dose of 550 mg/m2. Since Von Hoff's study, cumulative dose of anthracycline is a clinical factor that continues through today to predict the development of heart failure. While it has been suggested reduced doses decrease the chances of evolving heart failure.

After Von Hoff and colleagues' study, the successive studies measured changes in LVEF with anthracycline and confirmed a cumulative dose-dependent decrease in LVEF, particularly at cumulative doses of doxorubicin >350 mg/m2 (11,12). A multicentric trial study conducted among breast cancer patients instead which measured LVEF by equilibrium radionuclide angiography (ERNA) confirmed that 5.1% of the patients had evidence of CHF which was dose-dependent (13).

Other cardiotoxicity predictors include female gender, concurrent and prior treatment with cardiotoxic agents, age (> 65 years or < 18 years) (13), co-morbidities (renal failure, heart disease, systemic hypertension) (14) pre-treatment blood pressure, and body surface area (BSA) (15). Epirubicin is less cardiotoxic compared to doxorubicin (17–19), and the final cardiotoxic profile when no other anthracycline chemotherapy is co-administered may reflect a synergistic action (16). Altered metabolic profile related to anti-retroviral therapy) (17), promotion of endothelial activation and atheroma formation following systemic immune activity in Human Immunodeficiency Virus-infected patients increases their risk of cardiovascular disease (18,19) and the synergistic effect of these factors may be aggravated by anthracycline co-administration (17). Assessing the magnitude of and factors associated with anthracycline-induced cardiotoxicity among patients with breast cancer in the local setting is an instrumental way of upgrading departmental practice and supplementing the universal standard at the local level. Therefore, this study is intended to determine the prevalence of anthracycline-induced cardiotoxicity and associated factors as defined by a change in ejection fraction or development of CHF symptoms, associated with the current anthracycline-based regimen.

1.2 Literature Review

The history of chemotherapy use by human beings goes back to World War I when mustard gas was used as a chemical weapon and became known to be a potent suppressor of hematopoiesis (20). Currently, there are more than 100 cytotoxic drugs in use, as monotherapy or in combination therapy.

Cell mitosis or DNA synthesis (in the case of cells with short cell cycles) in cells are the most common target for chemotherapy drugs used in treatments. Anthracyclines are cytotoxic antibiotics and are among the most effective antitumor drugs ever developed. Since their discovery more than 50 years ago, anthracyclines have been used in the treatment of many cancers; solid tumors, soft tissue sarcomas, and hematological malignancies. (21,22)

Anthracyclines comprise a tetracyclic ring configuration linked to a sugar group. The most common anthracycline drugs are doxorubicin (DOX), daunorubicin (DNR), Epirubicin (EPI), idarubicin (IDA), pirarubicin, aclarubicin, and mitoxantrone.

Despite differences, after chemical structure, their biological characteristics and clinical application are remarkably diverse. As such, anthracyclines contribute to toxicity in healthy tissues and most notably chronic cardiomyopathy and congestive heart failure (CHF).(23,24)

The antitumor mechanisms of anthracyclines are numerous: Cross-linking of DNA, DNA alkylation, inhibition of topoisomerase II activity, inhibition of DNA replication and RNA transcription, generation of free radicals that cause DNA damage, and lipid peroxidation. In addition, anthracyclines interfere with the uncoiling of DNA and strand separation, and helicase activity and also cause direct membrane damage from lipid peroxidation (25) (26)

1.2.1 Left ventricular ejection fraction

Ejection fraction is the clinical quotient that is used to measure the amount of blood that left ventricles pumps out with each contraction, usually expressed in percentage.

In clinical practice, cardiotoxicity is detected by monitoring of LVEF which could be obtained from routine clinical examination or ECHO (27). Although these two methods merely detected asymptomatic cardiotoxicity, other tests are used to monitor anthracycline-

induced cardiotoxicities such as multi gated acquisition scan (MUGA) or equilibrium radionuclide angiocardiography, antimycin scintigraphy, tissue-doppler imaging, magnetic resonance imaging (MRI), endomyocardial biopsy, and indium-111 and biomarkers (28–31). However, LVEF is an important and universally accepted physiologic index of cardiac function. Evidence of heart failure induced by anthracycline cardiotoxicity is prefaced by a continued drop in LVEF. LVEF measures the volume of blood pumped out of the left ventricle with each contraction (32–35)

In Literature, Echocardiogram (ECHO) and MUGA scans are widely articulated ways used to detect anthracycline-induced cardiotoxicity (36–39). Most of the authors refer to the limited applicability of MUGA scans for frequent monitoring as a result of cumulative radiation exposure; however, when a precisely reproducible measurement is required for patient management decisions or clinical trial monitoring, MUGA may be the method of choice (36). A series of MUGA evaluations of LVEF varies from 2% to 4%, while a series of ECHO evaluations of LVEF varies from 13% to 17%. However, most studies in the literature have shown that reduction in LVEF of less than 10-points from baseline or decline below the institutional lower limit of normal is suggestive of anthracycline-induced cardiotoxicity (40–43).

After recent guidelines by the American Society of Clinical Oncology (ASCO), recommends measurement of the LVEF using ECHO for screening patients before and after initiation of any chemotherapy agents that induce heart toxicity. This ASCO recommendation further added that MUGA scans are the alternative method over ECHO in case ECHO is not available or precisely practicable with predilection given to MUGA (44).

It is recommended that succeeding investigation imaging and assessment of the LVEF depends on the chemotherapy dose and baseline cardiovascular risk factors. For example, higher doses of doxorubicin (250 mg/m2 or more), or the combination of lower-dose anthracycline (less than 250 mg/m2 of doxorubicin) needs subsequent measurement of the LVEF as compared to lower risk individuals who receive a lower dose (14,45,46).

Ejection fraction measurements and their interpretations – while a lowered LVEF indicates compromised cardiac function due to damaged cardiac muscle or disease, a patient with diastolic failure can have a normal or preserved ejection fraction (47). CF can either be attributed to systolic CF whereby the left ventricle muscle contracts inadequately resulting in reduced oxygenated blood being pumped throughout the body or to diastolic CF where contraction of the heart is normal but ventricles are impaired not allowing sufficient blood into the heart(34). Nevertheless, a patient with an EF of less than 35% is at risk of sudden cardiac arrest or cardiac death due to irregular heartbeats.

In the perspective of anthracycline-based chemotherapy, baseline LVEF is determined before treatment and again after three or four cycles where patients with an LVEF greater than 50% at baseline are deemed healthy and subsequently amenable to treatment (27)(34). However, a decrease in LVEF of greater than 10% from baseline to after treatment, or an LVEF of less than 50% may indicate the onset of cardiotoxicity, and treatment should either be discontinued or substituted (27,48). Moderate decreases (≤10%) in LVEF do not necessarily denote CF or impaired muscle function and may be stabilized with the discontinuation of treatment (61).

1.2.2 Prevalence of cardiac toxicity

Cardiac toxicity induced by anthracycline was first explained in a clinical trial study done in 1971 in sixty-seven patients with different cancer types who were given Adriamycin. Five patients developed CHF (50).

Doxorubicin-induced cardiotoxicity may range from asymptomatic electrocardiographic (ECG) changes to decompensated cardiomyopathy which is characterized by decreased left ventricular ejection fraction (LVEF)(51). Prevalence of acute and subacute cardiotoxicity is about 20-30%, and it is usually evident with transient ECG changes including nonspecific ST- and T-wave flattening, decreased QRS voltage, and prolongation of QTc interval, while chronic cardiotoxicity is associated with an irreversible nonischemic dilated cardiomyopathy (52).

A recent cross-sectional study done by Mulrooney et al. at St. Jude Children‘s Hospital in Memphis, Tennessee among 1833 adult survivors of childhood cancers, who had received anthracycline therapy by echocardiography found Cardiomyopathy, defined by LVEF of less than 50% was present in 7.4% (53).

In another study done in Belgium in 2011 among 77 patients of acute leukemia who were previously treated with Adriamycin, their echocardiographic results showed subclinical cardiac dysfunction among 30% of the study participants (54).

A multicenter study of more than 3000 breast cancer patients treated with cumulative doxorubicin doses of between 240mg/m2 and 360mg/m2 found that CHF occurred in about 1- 2% of the patients after 5 years (55). Additionally, the North Central Cancer Treatment Group(NCCTG) trial of between 2000 to 2005 which involved patients with breast cancer who had received four cycles of AC, found an asymptomatic LVEF drop of >10% but <15% compared with baseline range between 5% to 8.5% (55). In 1979, Von Hoff and colleagues assessed 4000 patients treated with AC retrospectively. They found the occurrence of CHF ranging from 2.2% to 7.1% (56). Moreover, the most recent studies have shown that the prevalence of LV dysfunction after ten years of follow-up in patients receiving AC is 63%(10).

In Tanzania, there is a dearth of data regarding the prevalence of cardiotoxicity that results from chemotherapy drugs, therefore this study seeks to determine the prevalence of anthracycline-induced cardiotoxicity among patients with breast cancer treated at ORCI.

1.2.3 Factors associated with anthracycline-induced cardiotoxicity

The cumulative dose of anthracycline has been widely articulated as the major risk factor for anthracycline-induced heart toxicity by many studies(77,18,78,76,79). While the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and many other trusted sources have specified that total cumulative doses of more than 550 mg/m² effects in irreversible cardiac damage, there are still patients who experience indications of cardiac failure below this prescribed “safe” anthracycline dose (13), On the other hand, there are also patients who can tolerate anthracyclines without incurring cardiotoxicity with cumulative doses higher than 1000 mg/m^2 (67)

Previous studies (61,68) the risks of cardiotoxicity credited to various varying cumulative doses and in some instances the type of anthracycline-based therapy. This suggests that there is no safe dose of anthracyclines and any attempt of dose-dependent association with cardiotoxicity might reduce the therapeutic advantage.

Advanced age has been long known as the risk factor for breast cancer, however, it has been further linked with the development of anthracycline-induced cardiotoxicity. (13,56,69). A former study done by Von Hoff that scrutinized a record of 4018 patients with a mean age of 49 years who were treated with doxorubicin, a steady increase in the risk of developing anthracycline-induced CHF was observed with increasing age ($P = 0.0002$) when comparing all age groups (56). Furthermore, the latest retrospective study has confirmed that age increases the likelihood of doxorubicin-induced congestive heart failure particularly at a cumulative dose of above 400 mg/m2 with patients older than 65 years having 2.25 times most likely to get congestive heart failure compared to those with age below 65 years (13). On the other hand, cardiotoxicity vulnerability with old age after treatment with Epirubicin was also noted in a prospective study that included 120 patients with advanced breast cancer. This study reported that patients with age greater than 50 years treated with Epirubicin cumulative dose of 1000 mg/m2 had a risk of 68% of declining LVEF (70,71)

Preexisting heart diseases are the potential predictors of anthracycline-induced cardiotoxicity. In literature, it has been proved by prospective and thematic studies that existing comorbidities such as hypertension, diabetes, and obesity substantially accelerates the actions of anthracyclines on heart muscles (56,72).

Overweight, (above 70kg) has often been reported as a potential risk factor for cardiotoxicity among patients with breast cancer treated with doxorubicin ($P = 0.005$) whereby high BMI (above 25Kg/m2) has been found to significantly correlate with the occurrence of left ventricular dysfunction after adjuvant Epirubicin-based chemotherapy in early breast cancer patients. (71).

Rate of administration: Peak serum concentrations of anthracyclines can be controlled in part by altering the rate of doxorubicin administration. Prolonged infusion therapy has been recommended to reduce anthracycline cardiotoxicity (73). This is supported by, a randomized control trial study that ascertained bolus administration of doxorubicin provided over 1 hour to 48 infusions for each of 12 dosages found no significant benefit (63).

The overall risk of ACT may be significantly increased when radiation therapy and/or other agents such as targeted drugs are utilized together with an anthracycline-based regimen. Radiation therapy, if administered in an irradiation field covering parts of the heart, may exacerbate symptoms of ACT and long-term cardiac risk – this is associated with a high cumulative anthracycline dose with radiation (64,66,73).

The risk of cardiac dysfunction increases from 10% to 28% when anthracyclines are combined with trastuzumab (27,47,74). Trastuzumab administered alone impairs myocyte contractility causing short-term, reversible damage; however, in combination with anthracyclines, it causes impairment to myocytes' homeostatic mechanisms and survival pathways ultimately contributing to myocyte loss and causing long term cardiac damage(47). Other potential contributors to cardiotoxicity include taxanes, platinum drugs, fluoropyrimidines, and Vinca alkaloids (75).

1.3 Conceptual Framework

The cumulative dose of anthracycline has long been articulated in literature as one of the major triggers of anthracycline related cardiotoxicity, In addition to a cumulative dose of anthracycline, way of administering (given a single injection or infusions that take over several hours) has also been spotted to potentially affect the risk of cardiotoxicity (76,77). however, there are other several factors that jointly or independently increase the chance of acquiring anthracycline-induced cardiotoxicity among cancer patients having anthracycline as one of the drugs in their chemotherapy regimen (78,79).

Older patients run risks of anthracycline-related cardiotoxicity due to lowered reserves of myocytes to compensate for the damage and therefore form the most vulnerable group (79). The role of gender as a risk factor for anthracycline-induced cardiotoxicity is still divisive female gender has traditionally been a risk factor for cardiotoxicity due to assumptions of a large accumulation of body fats which slows the drug clearance (80).

Patients with a history of heart disease or comorbidities such as diabetes and hypertension, liver and kidney dysfunctions have a high risk of developing anthracycline-induced cardiac dysfunction (81). Treatment with other cardiotoxic agents such as radiotherapy (82), paclitaxel (74,83), or trastuzumab (84) can also increase the risk of anthracycline-related cardiotoxicity.

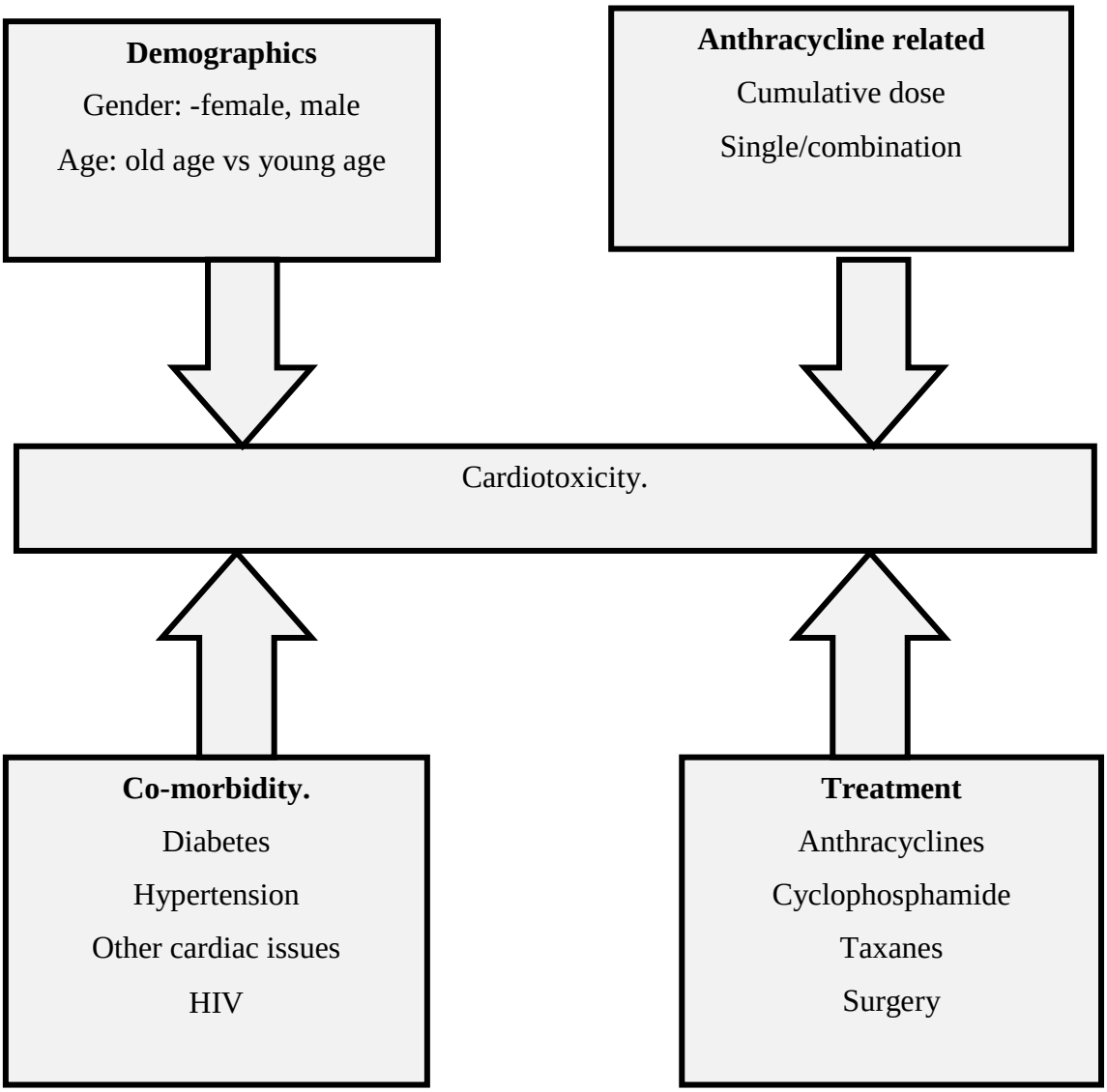

Figure 1: Conceptual framework

Source: Developed from the literature.

1.4 Problem Statement

Cancer survival rates have greatly improved in the last decade due to refined conventional treatments and the development of new therapies (85). However, improved survival has come at a cost; significant side effects are often related to treatment - cardiotoxicity being among the most serious (86,87). The cardiotoxic potential of anthracycline chemotherapy means that the focus of breast cancer treatment has been recast. As treatment most often involves anthracyclines, the aim is no longer to simply overcome malignancy: treatment now involves close monitoring of cardiac function before, during, and after their use (60,79,88–90). In Tanzania, there is a paucity of data regarding the assessment of LVEF in patients before and after anthracycline-based chemotherapy. Therefore, this study seeks to determine the prevalence of anthracycline-induced cardiotoxicity and associated factors among patients with breast cancer undergoing treatment at ORCI from Dec 2020-June 2021.

1.5 Rationale of the Study

This study seeks to fill the gap in knowledge on the prevalence and factors associated with anthracycline-induced cardiotoxicity in Tanzania. Previously, clinicians in Low middle-income countries have relied on data from high-income countries (HIC). The prevalence of AIC could be substantially different from that in HICs. A more accurate understanding of prevalence would be useful for planning individual patient care and preparing for the management of patients with anthracycline-induced cardiotoxicity.

Understanding factors associated with anthracycline-induced cardiotoxicity would help in designing interventions for preventing this adverse reaction or for selecting patients who are suitable for an anthracycline-containing regimen.

Therefore, this study shed light on the prevalence of anthracycline-induced cardiotoxicity as defined by a reduction in left ventricular ejection fraction, determine associated factors, among patients with breast cancer. This could ultimately provide the basics of adjusting the standard of practice in our local setting without compromising universal standards.

1.6 Research Questions

What is the prevalence of AIC and associated factors among patients with breast cancer undergoing treatment with anthracycline-containing regimens at ORCI from Dec 2020-June 2021?

1.6.1 Specific research questions

i. What are the social demographic and clinical characteristics of patients on treatment with an anthracycline-containing regimen for breast cancer at ORCI from Dec 2020-June 2021?
ii. What is the prevalence of anthracycline-induced cardiotoxicity among patients with breast cancer at ORCI from Dec2020-June 2020?
iii. What are the associated factors of anthracycline-induced cardiotoxicity as defined by a drop in LVEF among patients with breast cancer undergoing treatment with anthracycline-based chemotherapy at ORCI from Dec 2020 –June 2020.

1.7 Objectives

1.7.1 Broad objectives

The aim is to determine the prevalence of AIC and associated factors among patients with breast cancer undergoing treatment with anthracycline-containing regimens at ORCI from Dec 2020 to June 2021.

1.7.2 Specific objectives

i. To describe socio-demographic and clinical characteristics of patients on treatment with an anthracycline-containing regimen for breast cancer at ORCI from Dec 2020 to June 2021
ii. To determine the prevalence of anthracycline-induced cardiotoxicity among breast cancer patients treated with an anthracycline-containing regimen from Dec 2020 to June 2021at ORCI.
iii. To determine the factors associated with anthracycline-induced cardiotoxicity among patients with breast cancer undergoing treatment with anthracycline-based chemotherapy at ORCI from Dec 2020 to June 2021.

CHAPTER TWO

2.0 MATERIAL AND METHODS

2.1 Study Design

This was a single hospital-based cross-sectional study design.

2.2 Study Setting

This study was conducted at ORCI, the only specialized public tertiary hospital for cancer treatment in Tanzania. It has 22 consultant clinical oncologists 37 radiotherapists, 27 oncology nurses, and 6 medical physicists. Annually, hospital records show that ORCI receives around 540 breast cancer patients, with a monthly average of 40-50 cases. The center offers radiotherapy, nuclear medicine services, diagnostic radiological services, screening programs and cancer prevention, chemotherapy, palliative care, training, and research. It has a qualified radiologist trained in doing echocardiographs. It uses the current National Tanzania cancer guidelines with the following regimen in treating breast cancer (Doxorubicin / Epirubicin + cyclophosamide then Paclitaxel / Docetaxel) - AC-T (Cyclophosphamide, Doxorubicin / Epirubicin, Paclitaxel / Docetaxel - TAC (Cyclophosphamide, Epirubicin, 5 - fluorouracil) - CEF (cyclophosphamide, Methotrexate, 5-Fluorouracil) – CMF.

2.3 Target Population

All histologically confirmed cancer patients in Tanzania.

2.4 Study Population

All patients with histologically confirmed breast cancer on anthracycline-based chemotherapy attending ORCI outpatient clinic and meet eligibility criteria.

Specific inclusion and exclusion criteria are summarized below.

2.5 Eligibility Criteria

Inclusion criteria.

i. Patients newly diagnosed with histologically confirmed breast cancer.
ii. Patients who just completed the 4th cycle of anthracycline.
iii. Provision of informed consent

Exclusion criteria

i. Patients on trastuzumab (Herceptin).
ii. Prior history of chest wall radiotherapy.
iii. Those who decline to provide informed consent.

2.6 Sample Size Calculation

Using **Cochran's method**, the following formula assumptions were applied:

$$n = \frac{z^2 \times p \times (1-p)}{e^2},$$

p = Expected prevalence/rate, e= Margin of error/precision, n_0 is the finite population sample size, finite population sample size (required sample size) and Z is the level of confidence interval (CI).

The prevalence of AIC was estimated to be 9% based on a study conducted by Cardinale et al (2015)(91). Hence, the sample size formula is:

$$n = \frac{z^2 \times p \times (1-p)}{e^2} = \frac{1.96^2 \times 0.09 \times (1-0.09)}{0.05^2} = 126$$

2.7 Sampling Technique

A convenience sampling method was used. Patients who present to the general clinic and NHIF clinics and had been on an anthracycline-based regimen who meet the eligibility criteria were enrolled for the study. If patients met the present eligibility criteria at the follow-up clinic, then the patients were recruited, and the patient's LVEF was assessed using 2D Doppler echocardiography. The patient's social demographic factors, clinical profiles, and histopathological information were obtained from the patient's files and

supplemented by interviewing the patients. Cumulative anthracycline dose, route of administration was obtained from the consultant's prescription charts. Co-morbidities were assessed based on the patient's medical history.

2.8 Study Variables

The dependent variable of this study was Cardiotoxicity: defined as a decline in absolute-10% in LVEF from the baseline or LVEF less than 50% from normal value. This was assessed using ECHO immediately after completion of the 4th cycle of AC.

Table 1: Independent variables assessment plan

Variables	**Definition**	**Normal values**	**Cut off standard points.**	**Method of collection/assessment**
Co-morbidity; Diabetes	Group of metabolic disorders characterized by high blood sugar levels over a prolonged period	RBS 11.1m/mmol. FBS 5.5 m/mmol.	RBS > 11.1m/mmol FBS > 5.5m/mmol (Yes/NO)	Patient's medical history and random blood sugar.
Hypertension	long term medical condition in which the blood pressure in the arteries is persistently elevated	120 systolic 80 diastolic	>120 systolic >80 diastolic (Yes/NO)	Patient's medical history and measuring blood pressure on clinical visits.
Cardiac diseases.	Damage or disease in the heart's major vessels		Yes/No	The patient's medical history and baseline information from the Echo done

HAART	Are medication regimens used in the management and treatment of human immunodeficiency virus type 1 (HIV-1		Yes/No	
Demographics				
Body Mass Index	is defined as the body mass divided by the square of the body height, and is expressed in units of kg/m2,	18.5-25(normal weight)	< 18.5-(underweight)>25 (overweight	The patient's height and weight will be measured before treatment and calculated.
Alcohol Smoking	The inability to control drinking due to both physical and emotional dependence. Smoking is the action of inhaling or exhaling the smoke of tobacco that can affect health.		Yes/no	Interviewing and checking the patients' medical records.
Variables	Definition	Normal values	Cut off standard points.	Method of collection/assessment
Gender:	Female, Male		.	Interviewing patients and

				checking medical records.
Age:	Variant age groups		<40 , 41-60, 61+>	Interviewing patients and checking medical records.
Anthracycline related				
Cumulative dose		<250mg/m2	>350mg/m2	Checking prescription charts pre during treatment.
Drugs are given in combination				
Taxanes	Chemotherapeutic drugs are used in combination with anthracyclines to treat breast cancer.		Yes/No	Checking prescription charts prescribed during treatment**.**
Cyclophosphamide	Chemotherapeutic drugs are used in combination with anthracyclines to treat breast cancer.		Yes/No	Checking prescription charts prescribed during treatment**.**

2.9 Data Collection Tools and Collection Process

This study employed a questionnaire that consisted of two sections.

Sections A contained social demographic information, the clinical and histopathological profile of the patients.

This included age, gender, marital status, history of cardiac illness, education level, existing comorbidity, weight, height, chemo regimen and cumulative dose, stage, histological type, immunohistochemistry status.

The second section, B consisted of an echocardiogram assessment.

The diagnosis of cardiotoxicity was done by looking at the deviation of LVEF from the normal value. This was aided by using a SonoScape-S11 machine. One consultant radiologist who was also trained in performing echocardiograms at ORCI and a cardiologist from Jakaya Kikwete Cardiac Institute performed the ECHO on these patients during the study to minimize intra observer differences.

Before commencement of the study, the principal investigator recruited a research assistant who interviewed the participants about their social-demographic information and other information such as clinical and histological profiles from the records, files, or electronically stored. Principle investigator trained the research assistant on the research tools, data collection tools, ethical issues, and sampling procedures before the beginning of data collection.

2.10 Investigation tools, Validity, and Reliability

The following measures were used to ensure validity and reliability.

i. The main outcome measure (LVEF) was acquired after measurement on a reliable ultrasound machine that received regular service maintenance. The modalities of echocardiography that were used were of a two – dimensional real-time Doppler ECHO.

ii. The operator for the machine who measured the LVEF was a senior radiologist with significant experience in echocardiography at ORCI and a cardiologist at JKCI to reduce interobserver errors M-mode echocardiography investigations were carried out separately by different personnel using a uniform methodical protocol based on the set guidelines.

iii. A research assistant was recruited and trained to help in data collection.

2.11 Data Analysis

Data analysis was done using SPSS version 23 IBM. Categorical variables were summarized using frequencies while measures of central location and dispersion were used to summarize continuous variables. Logistic regression was conducted to determine factors associated with AIC. Factors with a p-value of less than 0.05 during bivariate analysis were included in the multivariate analysis. Factors with a p-value less than (0.05) were considered significant.

The table below shows the categorizations of independent variables

Table 2: Statistical analysis plan as per the specific objective

Specific objective	**Statistical analysis plan**
To determine the prevalence of anthracycline-induced cardiotoxicity in patients with breast cancer at ORCI from Dec-June2021	Frequency (percentage)
To describe demographic and clinical characteristics of patients on treatment for breast cancer at ORCI from Dec-June 2021	Frequency (percentage) Chi-square
To determine factors associated with anthracycline-induced cardiotoxic among patients with breast cancer undergoing anthracycline-based chemotherapy at ORCI from Dec – June 2021	Logistic regression

2.12 Ethical Consideration

The ethical clearance for conducting this study was sought from the Ethical Review Board of the Muhimbili University of Health and allied sciences. The permission to carry out the study was obtained from the Ocean Road Cancer Institute Ethical Review Board.

All participants were informed that their participation in the study was voluntary such that any time participants feel to withdraw from the study could do so without affecting his/her treatments. Patient anonymity was taken care of by numbering data collection tools while information that was collected was kept under lock and key sleeves. Patients who had cardiotoxicity were referred to Jakaya Kikwete Cardiac institute for Cardiologist/ physicians' review.

2.13 Consent Process

Advantages and disadvantages of participating in the study were communicated to the participants before recruitment, upon acceptance to participate in the study all participants were asked to fill the written consent form declaring their understanding of the study and voluntary participation and free withdrawal at any time in the study. The consent form had contacts of the PI, supervisor, and person from the MUHAS research and ethics committee where they could easily report any inconveniences.

2.14 Dissemination Plan

Upon completion of this dissertation paper, this paper could be presented at scientific conferences.

CHAPTER THREE

3.0 RESULTS

A total of 118 breast cancer patients on an anthracycline-based regimen from December 2020 through June 2021 at ocean road cancer Institute were enrolled in the study. The median age of study participants was 51.5 years; 99% (117) were females. Of the enrolled participants, 9.3% (11) were confirmed to have AIC through ECHO.

Table 3: Socio-demographic and clinical characteristics of patients on treatment with an anthracycline-containing regimen for breast cancer at ORCI from Dec 2020 to June 2021

Variable	Frequency	Percent
Gender		
Male	1	.8
Female	117	99.2
Age		
<40	22	18.6
41-60	75	63.6
60+	21	17.8
Marital status		
Married	86	72.9
Unmarried	32	27.1
Education		
Primary	50	42.4
Secondary	41	34.7
College/university	27	22.9
Alcohol		
Yes	11	9.3
No	107	90.7
BMI		
<25	102	86.4
25+	16	13.6
BSA		
<2.05	99	83.9
>2.05	19	16.1

Table 4: Socio-demographic and clinical characteristics of patients on treatment with an anthracycline-containing regimen for breast cancer at ORCI from Dec 2020 to June 2021

ECOG		
0	11	9.4
1	99	84.6
2	7	6.0
HIV status		
Positive	2	1.7
Negative	116	98.3
Hypertension		
Yes	28	23.7
No	90	76.3
Diabetics		
Yes	10	8.5
No	108	91.5
History of cardiac illness		
Yes	2	1.7
No	116	98.3
Baseline ECHO		
Baseline ECHO	20	14.5
Baseline & Post chemo ECHO	118	85.5

117(99%) of the recruited patients were female. Most of the patients were those with ages between 41-60, 75 (63.6%) with a median age of 51.5 years. Most of the participants were married 86(72.9%) and had attended primary school 50(42.4%). Only a few patients, 11(9.3%) reported the history of alcohol while 102 (86.4%) had BMI below 25kg/m2 One hundred and ten (94%) of the participants had ECOG below 1 whereas 2(1.7%) and 10(8.5%) were HIV+ and diabetic, respectively. Two patients (1.7%) had a history of cardiac illness. 118(85.5%) of the participants had both baseline and post chemotherapy ECHO.

Table 5: Clinico-histopathological information of the study participants

Variables	Frequency	Percent
Histopathology		
lobular	41	34.7
Ductal	70	59.3
Medullary+Mucinous+Papilary	7	5.9
Stage		
Early-stage	26	22.0
Late stage	92	78.0
Laterality		
Right	68	57.6
Left	50	42.4
Cardiac symptoms presentation		
Yes	4	3.4
No	114	96.6
IHC		
Luminal A	26	26.3
Luminal B	35	35.4
Basal like	29	29.3
Her2+	9	9.1
Missing's	19/118	16.1

Most of the participants, 70(59.3) were having infiltrating ductal carcinoma of whom 78 % were in an advanced stage. About 26 % were Luminal A, 35.4% were Luminal B, 29.3% were Basal like and 9.1% were HER2 positive. In terms of laterality, 68 (57.6%) of the participants had right-sided breast cancer. About four patients (3.4%) presented with cardiac symptoms.

Table 6: Treatment description of the study participants

Variable	Frequency	Percent
BCS		
Yes	10	8.5
No	108	91.5
Mastectomy		
Yes	68	57.6
No	50	42.4
Axillary Dissection		
Yes	63	53.4
No	55	46.6
Chemotherapy		
Adjuvant	78	66.1
Neo-adjuvant	40	33.9
Chemo regimen		
AC-T*	113	95.8
6TAC*	5	4.2
Cumulative dose (units)		
≤350	10	8.5
>350	108	91.5

*TAC Taxane, Adriamycin, Cyclophosphamide.

Majority of the patients (66%) were treated with surgery, 10 (8.5%) had breast conservative surgery (BCS) and 68(57.6%) had Modified radical mastectomy (MRM). Only 63(53.4%) had axillary dissection. Over half, 78(66.1%) of the participants received adjuvant chemotherapy and 33.9% received neo-adjuvant treatment. Most of the patients had a cumulative dose of anthracyclines of >350mg/m2. (91.5) and 8.5% received <350mg/m2.

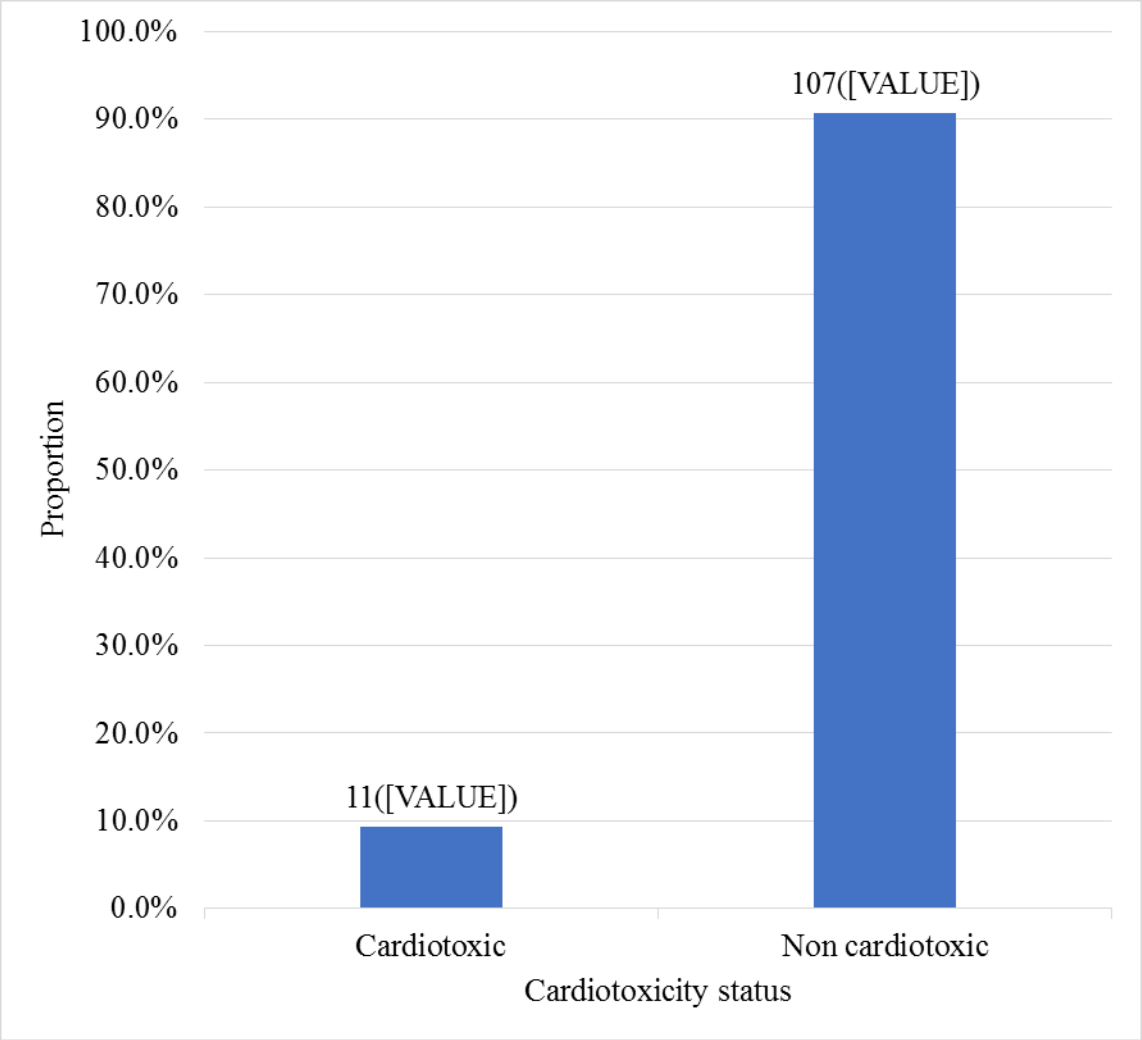

Figure 2: Prevalence of anthracycline-induced cardiotoxicity among breast cancer patients treated with anthracycline-containing regimen from Dec 2020 to June 2021at ORCI.

The prevalence of anthracycline-induced cardiotoxicity was relatively low. About 9.3% of the respondents developed Anthracyclines Induced Cardiotoxicity. The mean cumulative doxorubicin dose was 397mg/m^2 and had a standard deviation of 43.5. The minimum dose range was 288mg/m^2 and the maximum dose range was 520 mg/$m^{2.}$

Table 7: Bivariate analysis of the factors associated with anthracycline-induced cardiotoxic among patients with breast cancer undergoing treatment with anthracycline-based chemotherapy at ORCI from Dec 2020 to June 2021.

	Cardiotoxicity		
Variables	**Cardiotoxic N (%)**	**Non Cardiotoxic N (%)**	**P-value**
Gender			0.747
Male	0(.0)	1(100.0)	
Female	11(9.4)	106(90.6)	
Age			**0.040*** **
<40	1(4.5)	21(95.5)	
41-60	5(6.7)	70(93.3)	
60+	5(28.3)	16(76.2)	
Marital status			0.990
Married	8(9.3)	78(90.7)	
Unmarried	3(9.4)	29(90.6)	
Education			0.692
Primary	6(12.0)	44(88.0)	
Secondary	3(7.3)	38(92.7)	
College/university	2(7.4)	25(92.6)	
Alcohol			0.978
Yes	1(9.1)	10(90.9)	
No	10(9.3)	97(90.7)	
BMI			**0.001*** **
<25	6(5.9)	96(94.1)	
≥25	5(31.3)	11(68.7)	
BSA			0.520
≤2.05	8(7.9)	91(92.1)	
>2.05	3(17.6)	16(82.4)	
ECOG			0.420
0	2(18.2)	9(81.8)	
1	9(9.1)	90(90.9)	
2	0(.0)	7(100.0)	
Hypertension			0.075
Yes	5(17.9)	23(82.1)	
No	6(6.7)	84(93.3)	

Table 7: Continued

Variables	cardiotoxicity		P-value
	Cardiotoxic N (%)	Non Cardiotoxic N (%)	
Cardiac symptoms			**0.001*** **
Yes	3(75.0)	1(25.0)	
No	8(7.0)	106(93.0)	
Histopathology			0.465
lobular	2(4.9)	39(95.1)	
Ductal	8(11.4)	62(88.6)	
Medular+Mucinous+Papilary	1(14.3)	6(85.7)	
Stage			0.660
Early stage	3(11.5)	23(88.5)	
Late-stage	8(8.7)	84(91.3)	
Laterality			0.828
Right	6(8.8)	62(91.2)	
Left	5(10.0)	45(90.0)	
Mastectomy			0.088
Yes	9(13.2)	59(86.8)	
No	2(4.0)	48(96.0)	
Axillary dissection			0.177
Yes	8(12.7)	55(87.3)	
No	3(5.5)	52(94.5)	
Chemotherapy History			0.248
Adjuvant	9(11.5)	69(88.5)	
Neo-adjuvant	2(5.0)	38(95.0)	
Cumulative dose			**0.001*** **
≤350	3(30.0)	7(70.0)	
>350	8(7.4)	100(92.6)	
IHC			
Luminal A	2(7.7)	24(92.3)	0.185
Luminal B	6(17.1)	29(82.9)	
Basal like	1(3.4)	28(96.6)	
Her2+	0(.0)	9(100.0)	
Baseline ECHO			
Both baseline and post chemo	6(30.0)	14(70.0)	
Post chemo only	5(5.1)	93(94.9)	0.001

There was a significant association between age and development of AIC (P=0.04). Majority of the Participants 28.3% with age >60 had more AIC compared to 6.7% and 4.5% of 41-60 and ≤40 respectively. There was also a significant association between the presence of cardiac Symptoms and AIC (P value=0.001). Most participants 75% who had cardiac symptoms also had AIC compared to 7% of those who did not have symptoms of cardiac illness. Majority of the participants 31.3% who had BMI >25 had AIC compared to 5.9% of participants with BMI <25 (P=0.001). Most of the participants, 30% who received a cumulative dose of Adriamycin ≤350 experienced more AIC compared to 7.4% of those who received cumulative dose >350(P =0.001). Most

Luminal B (17.1%) developed cardio myotoxicity. Most of the patients who revealed cardiotoxicity were those who had baseline ECHO.

Table 8: Multivariate analysis on Factors associated with anthracycline-induced cardiotoxicity among patients with breast cancer undergoing treatment with anthracycline-based chemotherapy at ORCI from Dec 2020 to June 2021.

		95% C.I.for AOR
Variable	**P value**	**(Lower-Upper)**
Age		
<40		Reference
41-60	0.605	2.019 (0.141-28.875)
61+	0.158	7.338 (0.462-116.482)
BMI* **		
<25		Reference
≥25	0.032	6.086 (1.165-31.807)
Cumulative dose* **		Reference
≤350		
>350	0.045	0.080 (0.027-0.191)
Cardiac Symptoms* **		
Yes		Reference
No	0.002	0.012 (0.001-0.194)

In the Multivariate analysis: BMI, cardiac symptoms, and cumulative dose were found to be statistically significant. The chances of patients with BMI more than 25kg/m2 getting anthracycline-induced cardiotoxicity is 6.086 times higher than patients with BMI less than 25. There is a 92% lower risk of developing AIC when dose is less than 350mg/m2 than that of patients with a cumulative dose of >350. Patients with no cardiac symptoms have 0.002 times less chance of developing cardiotoxicity than patients with cardiac symptoms. Age was found to have no association with cardiotoxicity.

CHAPTER FOUR

4.0 DISCUSSION

Recently, the number of breast cancer patients surviving their cancer has kept on increasing due to improvements in therapies. Besides the marked rise in survival rate, lies the toxicities resulting from the treatment including cardiotoxicity (92).

The findings from this study demonstrated a prevalence of 9.3% of anthracycline-induced cardiotoxicity. It is the first cross-sectional study to examine the prevalence and associated factors among patients with breast cancer in Tanzania. Cardiotoxicity was described as LVEF of less than 50% or more than 10% decline of LVEF from the baseline ECHO. The patients in the index study that developed cardiotoxicity had no prior cardiac illness. Five patients (45%) that developed cardiotoxicity had hypertension. Patients that developed cardiotoxicity were treated by a mean cumulative dose of Adriamycin of 430±38mg while those who did not develop cardiotoxicity were treated by a mean cumulative dose of 394±43 mg. The prevalence of AIC in this study concurs with most studies which have shown that it ranges from 0.3% (93) to 56% (94). The variation in this prevalence could be attributed to the study design, the tool used and nature of the sample from the population i.e., children vs adult and type of cancer being treated, combination regimen, and several cycles received. This data is comparable to studies done on functional monitoring of anthracycline cardiotoxicity in Uganda and South Africa which reported a prevalence of 8.8% (95).

An increase in age was found to have an association in bivariate analysis though had no statistically significant association in the multivariate analysis. In this study, advanced age was found to be a risk for the development of anthracycline-induced cardiotoxicity. This finding is supported by one of the early studies conducted by Von Hoff et al. that scrutinized a record of 4018 patients with a mean age of 49 years who were treated with doxorubicin. It was shown that there is a steady increase in the risk of developing anthracycline-induced CHF with increasing age ($P = 0.0002$) when comparing all age groups (56).

The most cited reason was due to old age, elder patient's immunity and body metabolism slow down, and therefore the body cannot withstand such intensive treatment (59).

In this study, 30% who received a cumulative dose of Adriamycin ≤350 mg/m2 developed cardiotoxicity while 7.4% of those who received cumulative dose >350 mg/m^2 developed cardiotoxicity. The overall mean cumulative dose was 397mg/m2. According to early studies by Von Hoff et al., and Dolci et al. established that cumulative dose of doxorubicin increases the likelihood of AIC increase and they confirmed that doxorubicin-induced congestive heart failure is associated with a cumulative dose of above 400 mg/m^2 (13). Moreover, most recent studies (56, 59, 60, (96)) found that there is an increase in anthracycline-induced cardiotoxicity with an anthracycline cumulative dose of >350mg/m^2. The estimated risk of developing cardiotoxicity when doxorubicin is given 3 weekly is 1% to 2% at a cumulative dose of 330mg/m^2, 3-5% at a cumulative dose of 400 mg/$m^{2,}$ and 6-20% at a cumulative dose of 500 mg/m^2. When given in combination with Cyclophosphamide, taxanes, 5FU, and vincristine the risk are higher (27, 47, 72, 73) therefore ECHO monitoring of the patients at every cycle of anthracycline administration should be considered. The most likely reasons for the difference in the paradigm of cumulative dose threshold for AIC in this study might have been due to a small sample size used in this study and the short duration of follow-up. Moreover, this study revealed that cardiotoxicity was more (30%) among participants who had both baseline and post-chemotherapy echocardiogram than those who had an only post-chemo echocardiogram (5.1%) and since the majority (83.1%) of participants were lacking baseline echocardiogram, this might have potentially underestimated cardiotoxicity which in turn would reveal cumulative dose of >350mg/m^2 to have a higher proportion than those with ≤350 mg/m^2.

Findings from this study showed that the probability that patients with BMI more than 25Kg/m2 to develop anthracycline-induced cardiotoxicity was approximately 6.1 times higher than those with a BMI of less than 25 Kg/m2. Various other studies have reported a similar pattern (97). Fumoleau et al. found that high BMI above 25Kg/m2 significantly correlate (P = 0.005) with the occurrence of left ventricular dysfunction after adjuvant anthracycline-based chemotherapy (69).

A French CANTO cohort study that was aimed to seek the association of BMI and AIC in early breast cancer has also further suggested a 3-fold increased risk of developing cardiotoxicity, regardless of other predictors of cardiotoxicity (98). The likely reason for this has often been quoted to be due to increased body mass that leads to an increase in circulating blood volume and a compensatory increase in cardiac output at rest (99). (3)

Out of the Four patients that developed cardiac symptoms, 3 were found to have cardiotoxicity which was statistically significant (P=0.002). In literature, it has been proved by prospective and thematic studies that existing symptoms of heart problems could be triggered by anthracycline use to the full cardiac problem (56, 70). The finding of this study is relatively similar to a prospective cohort study that was done among 50 breast cancer patients in Aralık State Hospital, Gaziantep-Turkey on evaluation of early subclinical cardiotoxicity of chemotherapy in breast cancer which found 4% of the participants developed cardiac symptoms. Indication of cardiac symptoms during anthracycline treatment of breast cancer expresses immediate initiation of cardiac treatment (100).

The female gender has been found to have a significant risk of developing cardiotoxicity. In this study, gender was not associated with the occurrence of doxorubicin-induced cardiotoxicity. This could be due to the few numbers of male patients in the current study. Though the role of gender as a risk factor for AIC in adult cancer patients is controversial some authors suggested that the female gender is a potential predictor of anthracycline-induced cardiotoxicity posing mechanisms that females have high fat than males and since doxorubicin does not distribute to fat tissues, relatively higher doxorubicin concentrations can be absorbed in other tissues such as the heart (101)(102). Comorbidities and history of cardiac illness were not found to be associated with AIC this could probably be due to limited sample size.

CHAPTER FIVE

5.0 CONCLUSION, RECOMMENDATIONS, AND LIMITATIONS OF THE STUDY

5.1 Conclusion

This study demonstrated a prevalence of anthracycline-induced cardiotoxicity and associated factors among patients with breast cancer to be 9.3% within three months of completion of an anthracycline-based chemotherapy regimen. This data is similar to other studies done internationally. It also showed that the presence of cardiac symptoms, high BMI, and low cumulative anthracycline dose had an association with AIC.

5.2 Limitations

i. The majority of the patients only had an ECHO done after completion of chemotherapy (post-chemo) ECHO. If all the patients had both ECHO done at baseline and upon completion of chemotherapy, then more AIC would have been detected from the study population.

ii. The study period was short thus limiting the event of AIC to be observed.

iii. The study was limited by using a small sample size hence not possible to make the association between AIC with some demographic and clinical variables.

iv. We were unable to perform serial ECHO after every cycle to determine at what point the toxicity set in since it was a retrospective and cross-sectional study design.

5.3 Recommendations

i. More prospective studies should be done with a Multigated acquisition scan to assess how acute, early, or late cardiotoxicity manifests among patients with breast cancer since studies have shown it is the ideal tool for measuring cardiotoxicity.

ii. Cardiac symptoms had an association with AIC in this study therefore all cancer patients receiving anthracycline-based chemotherapy should have close monitoring of symptoms of HF, thorough cardiovascular examination, and cardiac evaluation of LVEF with ECHO at least before, during, and after completion of chemotherapy. This is especially important for patients who will receive both anthracyclines and trastuzumab thereafter radiotherapy.

iii. Elderly patients should preferably be treated by non-anthracyclines-containing regimen hence a need for more prospective studies to look into the association of age with AIC.

iv. A study needs to be done to assess how weight management among patients with breast cancer may be used to prevent anthracyclines-induced cardiotoxicity.

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APPENDICES

Appendix I: Informed consent form English version

TITLE OF STUDY: PREVALENCE OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY AND ASSOCIATED FACTORS AMONG PATIENTS WITH BREAST CANCER ATTENDING OCEAN ROAD CANCER INSTITUTE, DECEMBER 2020-JUNE 2021.

Principal investigator

Dr. Adagi Awuor Phiona
Resident Clinical Oncology
Phone: +255743750593
Email: phionaadagi@gmail.com

Purpose of study

You are being asked to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information. The purpose of this study is to determine the prevalence and predictors of anthracycline-induced cardiotoxicity among breast cancer patients who attended the ocean road cancer institute.

Study procedures

This study will require you to answer the question that you will be asked by the principal investigator or research assistant. An echocardiogram will be done upon completion of treatment to assess for the decline in LVEF. Your response will be written down in the prepared questionnaire and choosing not to participate will not affect your treatment.

Risks

No risk is expected for your participation in this study. You may decline to answer any or all questions and you may terminate your involvement at any time if you choose.

Benefits

If the Post chemotherapy echo finds you have a problem with your heart then you will be referred to see a heart specialist at JKCI. We are also hoping that the information obtained from this study may improve the standard of care at our institute.

Confidentiality

Your responses to this study will be anonymous. Participant data will be kept confidential except in cases where the researcher is legally obligated to report specific incidents.

Contact information

If you have questions at any time about this study, or you experience adverse effects because of participating in this study, you may contact the researcher whose contact information is provided on the first page. If you have questions regarding your rights as a research participant, or if problems arise which you do not feel you can discuss with the Primary Investigator, please contact me.

Dr. Bruno Sunguya: Director of research and publication, Muhimbili University of health and allied sciences P.O. BOX 65001, Dar es Salaam, Tanzania, Tel 255222-150-302-6/252489.

Voluntary participation

Your participation in this study is voluntary. It is up to you to decide whether to take part in this study. If you decide to take part in this study, you will be asked to sign a consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be destroyed.

Consent to take part in the research

- I.....voluntarily agree to participate in this research study.
- I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind.
- I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study.
- I understand that I will not benefit directly from participating in this research.
- I understand that all information I provide for this study will be treated confidentially.
- I understand that in any report on the results of this research my identity will remain anonymous. This will be done by changing my name and disguising any details of my interview which may reveal my identity or the identity of people I speak about.
- I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

_____ _____

Signature of participant Date

I believe the participant is giving informed consent to participate in this study

_____ _____

Signature of researcher Date

Appendix II: Consent form-Swahili version

Fomu ya idhini ya kujulishwa

Mada

Kiwango cha tatizo la moyo inyosabishwa na dawa za dripu za anthraksisi kwa wagonjwa wa saratani ya titi.

Mtafiti mkuu.

Dk Adagi Awuor phiona
Kliniki ya Onkologia
Simu: +255743750593
Barua pepe: phionaadagi@gmail.com

Malengo ya utafiti

Utambuzi wa upataji wa matatizo ya moyo pamoja na visababishi vyake kwa wagonjwa saratani ya ziwa wanaotibiwa na dawa za dripu ya anthraksia katika taasisi ya saratani ya ocean road.

Taratibu za Utafiti:

Utafiti huu utahitaji kujibu swali ambalo utaulizwa na mtafiti mkuu au msaidizi wa utafiti. Kipimo cha mishipa na misuli za moyo itafanywa kabla ya kupewa dawa za anthraksia ili kutathmini ufanyaji kazi ya moyo kabla ya kuanza matibabu na baada ya kumaliza matibabu. Jibu lako litaandikwa katika dodoso lililoandaliwa. Kuchagua kutoshiriki hakutaathiri matibabu yako.

Athari

Hakuna hatari yoyote inayotarajiwa kwako kushiriki katika utafiti huu. Unaweza kukataa kujibu maswali yoyote au yote na unaweza kumaliza kuhusika kwako wakati wowote ikiwa utachagua.

Faida

Ikiwa kipimo cha ufanyaji wa kawaida wa moyo baada ya matibabu utaonesha kuwa unatatizo la moyo basi utapewa rufaa kuona mtaalam wa moyo katika taasisi ya moyo ya

Jakaya Kikwete. Tunatumai pia kuwa habari inayopatikana kutoka kwa utafiti huu inaweza kuboresha kiwango cha huduma katika taasisi yetu.

Namba za mawasiliano

Kama utakuwa na swali lolote muda wowote kuhusu utafiti huu, au umepatwa na madhara yoyote kwa kushiriki kwako katika utafiti huu, unaweza kuwasiliana na mtafiti mkuu kwa number zilitolewa hapo juu katika ukurasa wa kwanza. Kama pia utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu au tatizo lolote limetokea ambalo unaona hauwezi kumshirikisha mtafiti mkuu, tafadhali wasiliana na dokta. Bruno Sunguya: Mkurugenzi wa maswala ya utafiti na uchapishaji wa tafiti katika Chuo kikuu cha afya na sayansi shirikishi cha Muhimbili, S.L.P 65001, Dar es salaam, Tanzania, Simu namba: 255222-150-302-6/252489.

Uhuru wa kushiriki

Ushiriki wako katika utafiti huu ni wa hiari. Ni juu yako kuchagua kushiriki katika utafiti huu. Ikiwa utaamua kushiriki katika utafiti huu, unatahitajika kutia saini fomu ya idhini. Baada ya kusaini fomu ya idhini, bado uko huru kujiondoa wakati wowote bila kutoa sababu. Kujiondoa kutoka kwa utafiti huu hakuathiri uhusiano ulionaona mtafiti. Ukijiondoa kwenye ushiriki katika utafiti huu kabla ya ukusanyaji wa data kukamilika, data yako itaondolewa katika kumbukumbu ya data za washiriki.

Kukubali

- Mimi _____Kukubali kushiriki katika utafiti
- Ninakubali kwa hiari kushiriki katika utafiti huu.
- Ninaelewa kuwa hata kama nakubali kushiriki sasa, naweza kujiondoa wakati wowote au kukataa kujibu swali lolote bila tatizo la aina yoyote**.**
- Ninaelewa kuwa naweza kuondoa ruhusa ya kutumia data kutoka kwa mahojiano yangu ndani ya wiki mbili baada ya mahojiano.
- Nimepata kusudi na asili ya utafiti ulivyonielezea kwa maandishi na nimepata nafasi ya kuuliza maswali juu ya utafiti.
- Ninaelewa kuwa sitafaidika moja kwa moja kwa kushiriki katika utafiti huu.

- Ninaelewa kuwa taarifa zote nitakazozitoa **kweny utafiti huu zitatunzwa kwa usiri mkubwa**
- Ninaelewa kuwa katika ripoti yoyote juu ya matokeo ya utafiti huu kitambulisho changu kitabaki bila majina. Hii itafanywa kwa kubadilisha jina langu na kuficha maelezo yoyote ya mahojiano yangu ambayo inaweza kufunua kitambulisho changu au kitambulisho cha watu ninaozungumza nao.
- Ninaelewa kuwa niko huru kuwasiliana na mtu yeyote aliyehusika katika utafiti ili kutafuta ufafanuzi zaidi kuhusu **utafiti huu.**

_____ _____

Sahihi ya mshiriki Tarehe

I believe the participant is giving informed consent to participate in this study

_____ _____

Sahihi ya mtafiti Tarehe

Appendix III: English version questionnaire.

Study Pro-Forma Document/Questionnaire

Study Title: PREVALENCE OF ANTHRACYLINE INDUCED CARDIOTOXICITY AND ASSOCIATED FACTORS AMONG PATIENTS WITH BREAST CANCER ATTENDING OCEAN ROAD CANCER INSTITUTE, Dec 2020- June 2021

No……. Date…….

A. Demographic Data

1. What is your AGE?

    1. < 40
    2. 41-60
    3. 60+

2. What is your sex?

    1=female.

    2=male

3. What is your marital status?

    1=Married

    2= Single

    3= widowed

    4=Divorced

    5= Separated

4. What is your level of education?

    1=Primary

    2= Secondary

    3= Tertiary

    4=College

    5= None

5. Do you smoke?
    1. Yes (Y) Pack years…..
    2. No (N0)…….
6. Do you have heavy alcohol consumption?
    1. Yes (Y) units/wk.……
    2. No (NO)……...
7. What is the BMI?
    1.<25
    2. >25
8. What is the BSA?
    1. <2.05 ……
    2. 2.06-2.57….
9. What Is the Performance status?

ECOG

    1. =0
    2. =1
    3. =.2
    4. =3
    5. =4
10. What is your HIV status?
    1. Positive (P)…….
    2. Negative (N)……
11. Are you ON ART?
        1. YES……
        2. NO…….

Comorbidities.

1. Have you ever been on treatment for any of these illnesses? (Yes/No)

    Hypertension……
    ……

Diabetes……

…….……

History of cardiac Illness …….……

Presence of Cardiac Symptoms……

2. Consent is given Yes……NO……

B. Pathology Information

1. Histology type?

    1. Invasive lobular Carcinoma
    2. Infiltrating ductal carcinoma
    3. Medullary carcinoma
    4. Mucinous (colloid) carcinoma
    5. Papillary carcinoma

2. Stage? 1….2….3….4……

3. Immunohistochemistry status?

    1. Estrogen

        1=Positive

        2= Negative1.

    2. Progesterone?

        1=Positive.

        2=Negative……

    3. Her 2

        1. Positive
        2. Negative

4. Laterallity?

    1. RIGHT …….
    2. LEFT….

C. Treatment History

1. Type of surgery?

A. Breast conservative Surgery? Yes….NO….

B. Simple Mastectomy? Yes….NO…...

C. Modified Radical Mastectomy? Yes…...NO….

D. Radical Mastectomy? Yes…...No….

E. Axillary lymph node dissection? Yes….NO…….

2. Chemotherapy History

A. Neo-adjuvant……

B. Adjuvant……

3. Regimen received?

A. AC

B. 4TAC……

4. Cumulative dose of anthracycline Received?

A. Doxorubicin

1. <350
2. .>350mg/m2……

5. ECHOCARDIOGRAM

Baseline

1. Present = P……..

2..Absent = A……..

Post

1. Present = P……..

2..Absent = A……..

ECHOCARDIOGRAPHYREPORT FORM

MEASUREMENTS:

Ao: (28 – 35 mm) LVIDd: (35 – 56 mm) IVSd: (06 – 12 mm)

LA: (28 – 36 mm) LVIDs: (24 – 42 mm) PWd : (08 – 13 mm)

EF: (50 – 70 %) ESV: ML EDV: ML

FS:

VALVES:

Mitral valve: MVA Valve thickness Stenosis: No/Yes Regurgitation: No/Yes Vegetation No/Yes

Aortic Valve: AVO Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes

Tricuspid Valve: ……. Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes

Pulmonary Valve: …… Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes.

CHAMBERS:

Left Atrium:

Right atrium:

Left Ventricle:

Right Ventricle:

SEPTAE: IVS **IAS:**

GREAT ARTERIES:

Aorta:

Pulmonary artery:

PERICARDIUM

Pericardial thickness: > 3 mm < 3mm Pericardial calcification: No/Yes

Pericardial effusion: > 3mm; 3 – 5 mm 5 – 10 mm > 10mm

OTHER FINDINGS:

Appendix IV: Swahili version questionnaire.

Zana ya Uchunguzi

1. Je! Umewahi kupata matibabu ya magonjwa yoyote haya?

    a) (Ndio la) Shinikizo la damu ……
    b) Kisukari ……
    c) Historia ya familia ya magonjwa ya moyo (sema ni ugonjwa upi)……
    d) Uwepo wa Dalili za Moyo ……
2. Idhini iliyopewa Ndio …… HAPANA ……

Jifunze Hati / Maswali ya Pro-Forma

Kichwa cha Utafiti: UPATAJI WA MATATIZO YA MOYO PAMOJA NA VISABABISHI VYAKE KWA WAGONJWA SARATANI YA ZIWA WANAOTIBIWA NA DAWA ZA DRIPU YA ANTHRAKSIA KATIKA TAASISI YA SARATANI YA OCEAN ROAD., DEC 2020- MAY

Namba…….

Tarehe…….

Taarifa za kijamii

1. Tarehe yako ya kuzaliwa ni ipi? .....

2. Je! Jinsia yako ni nini?

    1 = mwanamke;

    2 = kiume

3. Je! Hali ya ndoa yako ikoje? ....

    1 = Nimeoa/nimeolewa

    2 = Sijaoa/sijaolewa

3 = mjane

3 = Nimeachwa

4 = Talaka

5 = Tumetengana

5. Je! Una kiwango gani cha elimu?

1 = Msingi

2 = Sekondari

3 = Chuo Kikuu

4 = Chuo

5 = Sijasoma

6. Je! Unavuta sigara?

Ndio (N) Pakiti ngapi kwa mwaka ……

Hapana (H) …….

7. Je! Unakunywa pombe kupita kiasi?

Ndio (N) kisasi gani/ wk. ……

Hapana (H) ……

8.Kimo chako..... Uzito wako..... BSA…….BMI……

9. Je! Hali ya Utendaji ni nini? ECOG = 0… .1 …… .2 …… 3 …… .4 ……

10. Je! Una hali gani ya VVU?

Chanya (C) …….

Hasi (H) ……

11. Hali yako ya maambukizi ya ugonjwa wa ukimwi….Ndiyo/Hapana

12. Kama jibu lako ni Ndio je unatimia dawa…….. Ndiyo/Hapana

Zana ya Uchunguzi

1. Je! Umewahi kupata matibabu ya magonjwa yoyote haya? (Ndio/La)

    a) Shinikizo la damu ……
    b) Kisukari ……
    c) Historia ya familia ya magonjwa ya moyo (sema ni ugonjwa gani) ……
    d) Uwepo wa Dalili za Moyo ……
    e) Kupungua katika LVEF <50% za awali kabla ya matibabu……

2. Idhini iliyopewa

    NDIO….....……

    HAPANA ……..……

B. **Taarifa za Patholojia**

1. Aina ya saratani unayo? Titi la kushoto ama kulia ……

2. Hatua? 1… .2… .3… .4 ……

3. Daraja? 1… .2 …… 3 …… .4 …….

4. Hali ya immunohistochemistry? ER + ve…. / -ve …… PR + ve …… / -

ve …… Her 2 + ve… ... / - Ve ……

5.ziwa lililokuwa na tatizo ni la Kulia ……. kushoto

Taarifa za kumbukumbu za matibabu

1.upasuaji? kama ndio, aina gani

    A. Breast conservative Surgery? Ndio….Hapana….

    B. Simple Mastectomy? Ndio….Hapana….

    C. Modified Radical Mastectomy? Ndio….Hapana….

    D. Radical Mastectomy? Ndio….Hapana….

    E. Upauaji uliohusisha matezi za kwenye makwapa Ndio….Hapana….

2. Taarifa kuhusu kumbukumbu za dawa za dripu

A. Kabla ya upasuaji……

B. Baada ya upasuaji……

3.aina za dawa za dripu ulizopata?

A. AC

B. 4TAC……

3. Kiwango cha uongezekaji wa anthraksia iliyoingizwa mwilini?

A. Doxorubicin <350mg / m2 = …….> 350mg / m2 …….

B. Kipimo cha moyo cha altrasaundi

1. Taarifa za awali za kipimo cha moyo?

Zipo= Z …… .. Hazipo= H ……

2. Taarifa za kipimo cha moyo baada ya matibabu? Zipo= Z ……Hazipo= H

A. Tarehe iliyofanyika ……

B. Ilifanyikia wapi……

3. Uwepo wa kupungua kwa LVEF?

1.....LVEF <50% ……. LVEF> 50% .....

FOMU YA RIPOTI YA ECHOCARDIOGRAPHY

ECHOCARDIOGRAPHYREPORT FORM

MEASUREMENTS:

Ao: (28 – 35 mm) LVIDd: (35 – 56 mm) IVSd: (06 – 12 mm)

LA: (28 – 36 mm) LVIDs: (24 – 42 mm) PWd : (08 – 13 mm)

EF: (50 – 70 %) ESV: ML EDV: ML

FS:

VALVES:

Mitral valve: MVA Valve thickness Stenosis: No/Yes Regurgitation: No/Yes Vegetation No/Yes

Aortic Valve: AVO Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes

Tricuspid Valve: ……. Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes

Pulmonary Valve: …… Stenosis: No/Yes Regurgitation: No/Yes Vegetation: No/Yes.

CHAMBERS:

Left Atrium:

Right atrium:

Left Ventricle:

Right Ventricle:

SEPTAE: IVS **IAS:**

GREAT ARTERIES:

Aorta:

Pulmonary artery:

PERICARDIUM

Pericardial thickness: > 3 mm < 3mm Pericardial calcification: No/Yes

Pericardial effusion: > 3mm; 3 – 5 mm 5 – 10 mm > 10mm

OTHER FINDINGS: