PREVALENCE, RISK FACTORS AND MANAGEMENT OF VENOUS THROMBOEMBOLISM AMONGST PATIENTS UNDERGOING BREAST CANCER TREATMENT AT KENYATTA NATIONAL HOSPITAL

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DEDICATION

This dissertation is dedicated to my Lord and Savior Jesus Christ for granting me the strength and wisdom to see it through. To my parents, Samuel and Mellen Asiago, pillars of my life brothers Geoffrey and Edgar and my sister Mercy for the unwavering support they have afforded me. Finally, to Pauline the calm in my stormy days.

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LIST OF ABBREVIATIONS AND ACRONYMS

5-FU	5 Fluorouracil
a PTT	Activated Partial Thromboplastin Time
ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
AOR	Adjusted Odds Ratio
ASCO	American Society of Clinical Oncologists
BMI	Body Mass Index
CAT	Cancer-Associated Thrombosis
CCI	Charlson Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
COR	Crude Odds Ratio
DOACs	Direct-Acting Oral Anticoagulants
DM	Diabetes Mellitus
DTP	Drug Therapy Problem
ERC	Ethics and Research Committee
GCO	Global Cancer Observatory
HER2	Human Epidermal Growth Factor Receptor 2
HRT	Hormone Replacement Therapy
IARC	International Agency for Research on Cancer
ITAC	International Initiative on Thrombosis and Cancer

KNH	Kenyatta National Hospital
LMWH	Low-molecular-weight heparin
MDT	Multi-Disciplinary Team
MOH	Ministry of Health
MRP	Medication Related Problem
NCCN	National Comprehensive Cancer Network
NCD	Non Communicable Disease
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
UHF	Unfractionated Heparin
UoN	University Of Nairobi
WHO	World Health Organization

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DEFINITION OF TERMS

Breast cancer

Breast cancer is an irregular development of cells (a gathering of disease cells) emerging from the cells found in the breast. Breast cancer also denoted in this study as breast cancer commonly occurs in women, but it has also been known to affect men. (1)

Chemotherapy

Chemotherapy is characterized as the utilization of any medication for the management of any disease. For this study, the word chemotherapy was utilized to mean the medications used for the management of cancer disease. Chemotherapy works all through the body. This implies chemotherapy can kill cells causing cancer that has metastasized to other body parts far from the original tumor site. However, medical procedures and the use of radiation treatment eliminate, destroy, or harm malignant cells in certain zones. (2)

Hyper-coagulable state

In the study, the study participants were be said to be in a hyper-coagulable state if they will have abnormalities in their laboratory readings or clinical conditions that are related to more risk of thrombosis or if they have repeated thrombosis episodes without recognizable predisposing factors to VTE. (3)

Deep vein Thrombosis

Deep vein thrombosis (DVT) normally arises in a vein deep inside the legs, or sometimes in bigger veins that run over the muscles of the thigh and calf muscles. It normally causes painful swelling in the leg which may lead to complications like pulmonary embolism. (4)

Pulmonary Embolism

Pulmonary embolism (PE) normally emerges when a blood clot loosens up and travels through the circulatory system to the lungs. (4)

Venous thromboembolism

Venous thromboembolism (VTE) is a disorder in which, because of the blood being in a hyper-coagulable state, prompts blood clotting and blood clots will form. This coagulation is frequently formed in the deeper veins situated in the leg, groin, and arms. This is known as deep vein thrombosis (DVT). In the event that the clot moves in the circulation, and stalls out in the lungs, it is known as pulmonary embolism (PE).

ABSTRACT

Background

Breast cancer is the second most common malignancy and cause of cancer-related mortality. Cancer has long been associated as a risk factor for hyper-coagulation. It may, therefore, lead to venous thromboembolism in breast cancer patients. Venous thromboembolism is a major risk factor, accounting for the second most common cause of cancer-associated mortality. This has made the management of coagulation in cancer to be both complex and also important.

Objective

The purpose of this study was to establish the prevalence, risk factors, and management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Research Methods

The study adopted a cross-sectional study design and was conducted at the Kenyatta National Hospital-oncology department. Three hundred and seventy seven patient's files which fitted the inclusion criteria were sampled by using simple random sampling technique. Data on the patient's sociodemographic characteristics, tumor and chemotherapy-related factors were collected by using a predesigned data collection tool. The data was then checked for completeness and data quality. It was then organized, coded and analyzed using STATA version 13. Univariate analysis was done by use of descriptive statistics using mean, median and standard deviation. The risk of developing a venous thromboembolism was assessed by using the Khorana risk assessment tool. Additionally, the strength of association between the predictor and outcome variable was assessed by the use of inferential statistics with a p- value of less than 0.05 considered to be statistically significant.

Results

The number of patients who were found to have venous thromboembolism was 10 (2.65%). Age was found to be a significant risk factor for the development of venous thromboembolism (p= <0.001). (AOR=0.47; CI=0.24-0.94; p=0.032). Surgery done in the last one year was also found to be a predictor of the risk of having a venous thromboembolic event. (AOR= 0.68;

CI=0.48-0.98; p=0.04). The duration it took to initiation of chemotherapy since diagnosis and the number of chemotherapy cycles were also found to be significant predictors of risk of developing a venous thromboembolic event at (p=0.012) and (p=<0.001) respectively. (AOR= 1.64; CI=1.1-2.44; p= 0.015). Additionally, there was a statistically significant association between the use of radiotherapy and the risk of developing a venous thromboembolism (p=<0.001). (AOR=0.09; CI=0.03-0.24; p=0.001). Warfarin and Low molecular weight heparin were commonly used for the management of venous thromboembolism as depicted by 8(80%) of the patients who were managed by using these two agents.

Conclusion

There is a high prevalence of venous thromboembolism amongst breast cancer patients. Several predictors of the risk of the development of venous thromboembolism were identified in the study. This included the number of chemotherapy cycles, age of the breast cancer patient, use of radiotherapy and surgery in management, and the number of months since breast cancer was first diagnosed. All these risk factors need early detection to enable them to be adequately managed.

Recommendation

The use of venous thromboembolism risk models should be further explored and used to educate patients who are on a higher risk about the warning signs and symptoms of venous thromboembolism. In addition, modifiable risk factors for the development of a venous thromboembolism should be identified early adequately managed.

CHAPTER 1: INTRODUCTION

1.1 Background

Breast cancer is a disease of the breasts in which the cells of the breasts grow out of control. While early screening and self-examination are encouraged, breast cancer keeps on being exceptionally prevalent, particularly in women. Different risk factors that have been attributed to causing the advancement of breast cancer include alcohol abuse, age, hormones and being overweight or obese. (5)

Consequently, the management of breast cancer has become important. Breast cancer can be managed by the use of various methods. These methods include chemotherapy, surgery, hormonal therapy, radiation therapy, and biological therapy. Usually, a combination of these methods is used in management. (6) However, the utilization of these methods for cancer management has been linked to a greater risk of coagulation. (7) Other factors that have been shown to escalate the risk of venous thromboembolism among breast cancer patients include the type of cancer involved, advanced disease, any previous or current surgery and hospitalization. (8)

Cancer has long been associated as a risk factor for hyper-coagulation. As a result of the blood clotting, it may lead to pulmonary embolism or at times deep vein Thrombosis (DVT) in breast cancer patients. Consequently, the incidence of blood clotting has been a common cause of death amongst breast cancer patients. (9) This has, therefore, made the management of coagulation in cancer to be both complex and important.

1.2 Problem Statement

Cancer of the breast is the second commonest malignancy and cause of death amongst all the malignancies. It is the top cancer in women worldwide with an upward trend particularly in both developing and developed countries. (10) Consequently, breast cancer has become a burden in developing countries including Kenya. This is due to due to breast cancer-associated mortalities and morbidities which mainly affect women. (11)

Cancer itself has been shown as a noteworthy cause of hyper-coagulable state in cancer affected patients. Breast cancer is no exception to this and has, as a result, led to venous thromboembolic events (VTE). VTEs are primarily classified into Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT). (12) The management of VTE in cancer has however proved to be challenging mainly due to higher rates of VTE recurring episodes as well as a higher risk of bleeding with anticoagulation treatment. (8)

Consequently, as a result of this, VTE has turned out to be one of the most common reasons for mortality amongst cancer patients. This can be attributed to the utilization of drug therapy for the management of breast cancer. It has been demonstrated that chemotherapy posed as an independent risk factor for the development of VTE. (13) The patient-friendly direct oral anticoagulants (DOACs) that are commonly used may offer an alternative to other therapies; however, data in cancer patients and direct comparisons to the current standard of care with low molecular weight heparin (LMWH) are limited. (14) In addition, little is known about the optimal duration of VTE treatment in malignancy or how to treat patients who experience recurrent thrombosis despite LMWH. In this regard, with relatively few studies done on cancer-associated VTE done in Kenya, there is a need to find the occurrence, risk factors involved and management of VTE in the population. (3)

1.3 Research Questions

1. What is the prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital?
2. What are the risk factors associated developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital?
3. Which methods are used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital?

1.4 Objectives

1.4.1 Main Objective

The purpose of this study is to establish the prevalence, risk factors, and management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

1.4.2 Specific Objectives

1. To establish the prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.
2. To evaluate the risk factors associated with developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital.
3. To identify the methods of managing venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

1.5 Justifications of the Study

Venous thromboembolism is a major risk factor for mortality. They account for the second commonest cause of death amongst cancer afflicted patients worldwide after cancer itself as a cause of death. This may be attributed to the fact that patients with cancer are in a state of hyper-coagulation. As a result, they are at a higher risk for the development of VTE during the course of their illness compared to those without cancer. This VTE may advance and appear as any of DVTs and or PE. Incidence of venous thromboembolism occurring in a patient is usually linked with a progressed stage of cancer and a poor prognosis especially if diagnosed together with or within one year of the VTE incident. (15) Therefore, it's very important to do a routine examination to pinpoint patients who have a greater chance of developing VTE which this study will help to identify.

The hypercoagulability may also be attributed to various other factors including hospital admissions, surgery, the use of catheter and chemotherapy. (13). However, despite its prevalence in breast cancer, the rationale for the use of anti-coagulants as prophylaxis to help reduce the incidences of VTE has not been recommended. However, this is a risk in itself that needs to be considered, as well as the diversity of breast cancer patients, which does not

rationalize universal administration of thrombo-prophylaxis as use of anti-coagulants as this may also lead to excessive bleeding. As a result, this may pose a danger to the patient too.

There is, therefore, a need to strike a balance between the provision of oral anti-coagulants for prophylactic and management of VTE in people with a high risk of breast cancer. Nevertheless, till now, a reliable tool for the assessment of risk in patients on anticancer treatment for common solid cancer growths remains an unmet medical need at Kenyatta National Hospital (KNH) which this study hopes to address. Another advantage is that the risk of VTE was reported on the basis of easily confirmable and time-dependent risk factors, which was the basis for suitable patient management.

In this regard, it is also imperative to have a clear well-defined pathway in the management of VTE in breast cancer patients. This study will help to address that by giving direction on the best approach to use in the management of VTE episodes amongst breast cancer patients and hopefully other malignancy disorders. By so doing, it will help in the reduction of a variety of approaches in the management of VTE in breast cancer patients.

1.6 Significance of the study

By doing this study, the investigator hopes to determine the occurrence of VTEs amongst breast cancer patients. By highlighting this, the plight of these disorders will be better addressed hence reduce the burden of disease and hopefully have an impact by reducing the mortalities attributed to venous thromboembolism amongst breast cancer patients. This study will help reduce the occurrence of venous thromboembolism by timely identification of clients at high risk by prompt screening for the risk factors linked with the progression of venous thromboembolism. By identifying the risk factors, they may be better addressed and hence help mitigate the incidence of coagulation amongst the population. In addition, it will also help highlight the management methods for venous thromboembolism. By so doing, the study may identify any gaps in the treatment of VTE in breast cancer and guide the best way to manage them and give the best possible treatment outcomes to the patients.

1.9 Conceptual Framework

The incidence and severity of breast cancer can due to a multitude of reasons, these include the patient characteristics like the gender, age, various other co-morbidities and elevated BMI

(Body Mass Index). Tumor related factors like where the cancer is located, tumor histology and the stage of the cancer may also cause a rise in the prevalence of VTE events in breast cancer patients. Finally, chemotherapy factors like the cancer therapy being administered, raised pre-chemotherapy platelet count, higher pre-chemotherapy leukocyte count and the use of erythropoiesis-stimulating agent have been known to be contributory factors to the development of venous thromboembolic events.

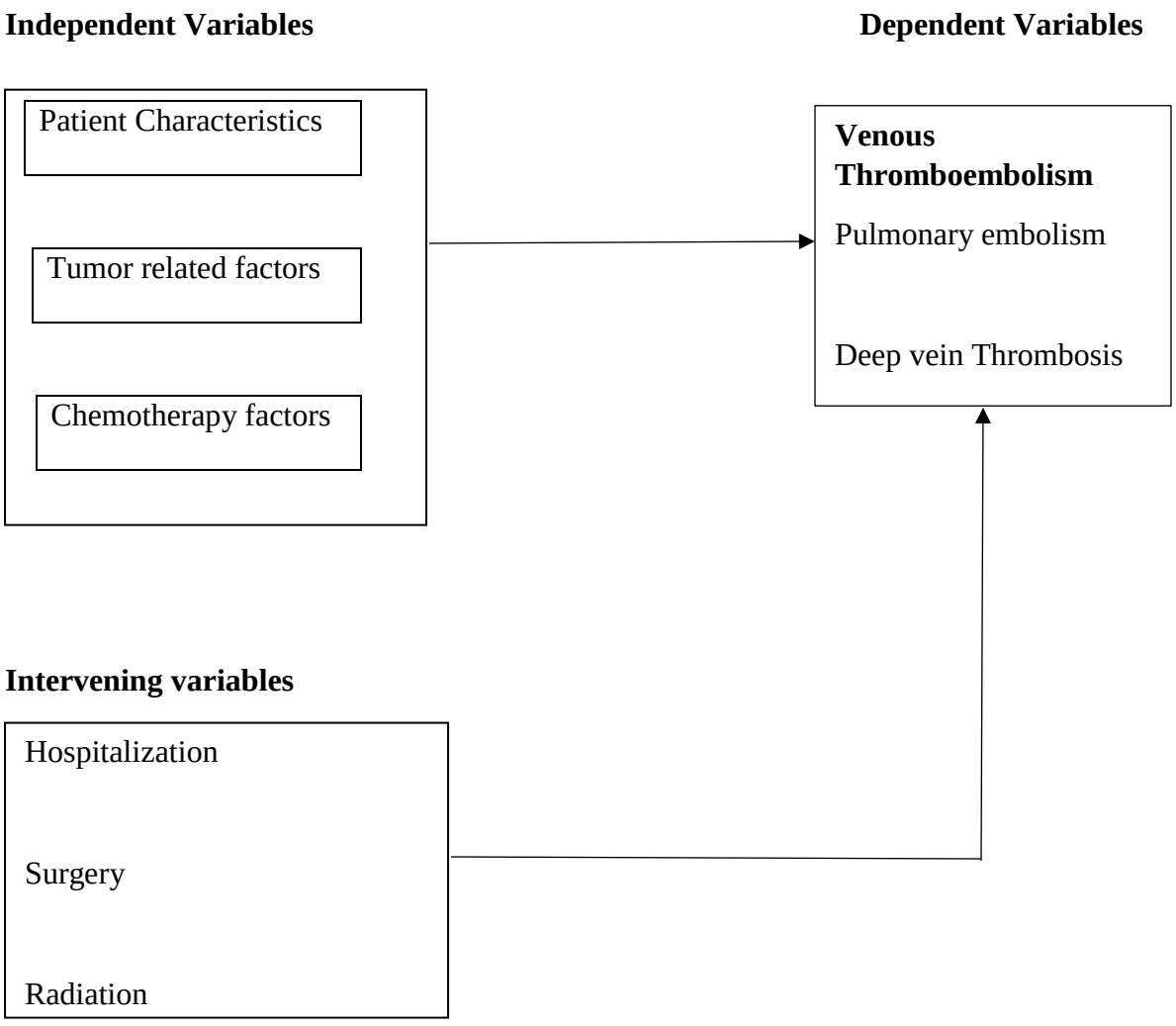

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Figure 1: Conceptual framework

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This literature review intends to look at the prevalence of breast cancer. It will first give an overview of the various types and stages of breast cancer. Thereafter, it will give a worldwide perspective on the prevalence of breast cancer then narrow down to Africa, the sub-Saharan region and then finally, Kenya. It will then look at the risk factors linked with the progression of VTE. Finally, the literature review intends to delve into the methods that are utilized for the management of VTE in breast cancer patients.

Breast cancer is a malignant tumor arising from the cells of the breast. Most breast cancers are adenocarcinomas. Breast cancer can be classified based on the type, breast cancer grade, and stage or gene expression. They may be ductal or lobular, invasive or non-invasive. (17) The various types of breast cancer include infiltrating ductal carcinoma, lobular carcinoma in situ, infiltrating lobular carcinoma, medullary carcinoma, mucinous (colloid) carcinoma, tubular carcinoma of the breast, papillary carcinoma, metaplastic breast cancer, and mammary Paget's disease. (17)

With the American Joint Committee on Cancer (AJCC) staging being the most common method of classification of breast cancer, the principal researcher will use this method in this discussion. (18) The stages of breast cancer discuss the extent and evolution of breast cancer. Stage 0 cancers are also called carcinoma in situ. These cancers have not grown in the stroma, nor have they spread into the tissues. (19) Non-invasive cancer, though cancer, is considered stage 0. There are three types of stage zero carcinoma of the breast. They are Ductal carcinoma in situ (DCIS) which mainly occurs in the ducts, Lobular carcinoma in situ (LCIS) which occurs in the lobules and finally, Paget disease of the nipple. (17)

Stage 2 cancer implies that breast carcinoma is developing, but it is however limited to the mammary glands or its spread has only extended to the nearby lymph nodes. This phase is further sub-divided into two groups: Stage2A and Stage 2B. The variation between the stages

of stage 2 breast cancer is determined by the size of the tumor and whether the breast cancer has spread to the lymph nodes. (17)

Breast cancer can be referred to as stage 3 breast cancer if it has extended to several lymph nodes which are nearby. Breast cancer can be described as stage 3 if the tumor is bigger than five cm and the malignancy has extended to any lymph nodes but has not reached far off organs. It is also divided into three sub-phases. (17) If a patient has stage 4 breast cancer, this implies that the malignant cells have metastasized various other parts of the body, like the lungs, lymph nodes, bones, skin, liver, or brain. (20)

2.2 Prevalence of breast cancer

Breast cancer is mainly seen among women than men. In fact, 98% of breast cancer is commonly seen in women as compared to men. (21) In developing nations, it has mainly been attributed to late diagnosis. However, the late diagnosis doesn't mean that it is only observed in older women. The late-manifestation tendency is slowly evolving and in some parts, more women are presenting early with the disease. (11) The number of new cases of in situ breast malignancy has increased mainly because of the extensive use of mammography for breast cancer diagnosis. (22)

When comparing the risk females in the universal population have of developing first primary breast cancer and females with a history of stage zero breast cancer, those with stage zero breast malignancy are at a substantially higher danger of getting second primary breast cancer. (23) The likelihood of a second primary in situ tumor is 4.2- to 7.2-fold higher and the danger of a second primary invasive breast malignancy is 3.4- to 8.6-fold higher in situ breast cancer survivors compared with women in the universal population (24). The possibility of a second primary breast cancer among in situ breast cancer survivors varies with patient and clinical characteristics, although current epidemiologic evidence is limited. (25)

Breast cancer is the foremost reason for malignancy-related death amongst females, leading to every one in four cancer-related deaths in the world. It ranked as the fifth prominent cause of mortality accounting for 627,000 deaths which were 6.6% of the total population. (22)(10)

A broader look indicates that there was an upsurge in the worldwide cancer burden. This was projected to have increased to 118.1 million new cases by the year 2018. This is in addition to 9.6 million deaths which occurred in 2018. (22) The increased burden was attributed to various factors like the growth in the population and aging as well as the ever-changing prevalence of various causative factors of cancer. These prevalence have been linked to social developing economies especially in fast-growing economies, where a change was observed from malignancies related to poverty and infections to cancers associated with the population's way of living. (5) Almost 50% of the incident cases detected together with a little over half of the cancer deaths worldwide in 2018 are estimated to have occurred in the Asian region. However, this was partially attributed to the reason that the region contained nearly 60% of the total of the world's population. (23)

In Africa, Cancer accounted for 5.8% of all cancer-related deaths in the world. Of this figure, breast cancer had an incidence of 168,690 new cases and mortality of 74,072 in the year ending 2018. Predictably, the Asian region took the largest share because of its large population as compared to the other continents. (26)

Closer to home, in East Africa, Ethiopia had the largest incidence of breast cancer at 15,244 new cases which accounted for 37.8% of all the female breast cancer patients in Eastern Africa leading to 8,159 which was 40.5% of all breast cancer deaths in 2018 in East Africa. (22) Worryingly, Kenya ranked second in the number of incident cases of breast cancer in eastern Africa with 5,985 new cases and 2,553 deaths which were 12.7% of all breast cancer deaths in Eastern Africa. There was no sufficient data on breast cancer amongst males in Africa, East Africa or Kenya. (10)

Studies on the prevalence of VTE amongst breast cancer patients are rare. A study by Khorana found out that cancer-associated VTE is a significant reason for death in patients receiving active therapy for cancer. Other comparatively smaller groups of females receiving chemo for breast cancer, risks of VTE have ranged from 5.5% to 8.0% amongst females with local and regional disease.(27) Additionally, the rates which were reported are possibly underestimated, as post-mortem studies show that the number of new cases of PE in cancer patients that was higher than clinical rates which were suggestive VTE. (28)

The use of VTE prophylaxis has been shown to decrease the risk of getting a VTE event of pulmonary embolism or Deep vein Thrombosis. A Cochrane review on anticoagulant prophylaxis to prevent asymptomatic DVT in hospitalized medical patients showed that anticoagulant prophylaxis provided a 49% reduction in the risk for symptomatic DVT in medical patients who were at risk with most of these events occurred during the first month after discharge from hospital. This may have suggested that many of the formed thrombi are silent during hospitalization and become evident after discharge. (29)

2.3 Risk factors for the development of VTE amongst breast cancer patients

Breast cancer has been recognized as an independent risk for the development of VTE. (7) The hypercoagulability state in breast cancer usually involves several multifaceted and interdependent mechanisms, these include interaction among the cancer, host cells, and the coagulation system. Advanced stage of malignancy and a poor prognosis of cancer usually occurs if the cancer is diagnosed concurrently within one year after an incident of VTEs. (30) The danger of VTE is four to seven times more in breast cancer patients than in those without breast cancer. (31) As a result, VTE has been known to also be a major reason for morbidity and death in patients with cancer. (3)

In the outpatient setting, patient risk assessment can be conducted based on a validated risk assessment tool like the Khorana Risk assessment tool, Vienna Score, Protach score and the Caprini score. (16) (32) The principal investigator intends to use this model in this study. This validated model was preferred because it can identify patients with a nearly 7% short-term risk of symptomatic VTE and therefore a good indicator of possible Venous thromboembolic events. (33) This model can be used for predicting chemotherapy-associated VTE using baseline clinical and laboratory variables. The most common baseline variables that are used include the site of cancer where 2 points are awarded for very high-risk site and 1 point for high risk site, the platelet count of 350×10^9 / Litre or more, hemoglobin level less than 100 g/L (10 g/dL) and or use of erythropoiesis-stimulating agents, leukocyte count more than 11 $\times 10^9$ /L, and body mass index of 35 kg/m^2 or more (1 point each). In this case, the pre-chemotherapy platelet count, hemoglobin level and pre-chemotherapy leukocyte count were each awarded one point in the score. (32)

There are several factors that lead to the risk of developing VTEs. These factors occur together in cancer patients. They may include hospitalization, the presence of an indwelling catheter, surgery, use of erythropoiesis-stimulating agents (ESAs), chemotherapy, and new molecular-targeted therapies such as antiangiogenic agents. (15) (13) For the sake of this study, the investigator discussed the risk factors that lead to the development of Venous Thromboembolism among breast cancer patients in three major areas namely: patient characteristics, tumor-related factors, and chemotherapy-related factors. (8)(34)

2.3.1 Patient Characteristics as risk factors for the development of VTE amongst breast cancer patients

The various causes of the development of VTE in breast carcinoma include age, BMI, a history of VTE, gender and any other underlying comorbidities. Because of the presence of estrogen in females, breast cancer is more prevalent in females than in males. (29) This is because of the endogenous estrogen produced by the ovary in premenopausal women. It, therefore, goes that surgical removal of the ovaries may help to minimize the danger of getting breast cancer. The leading sources of exogenous estrogen are the progestin-only pills and combined oral contraceptives which are the oral contraceptives commonly used for family planning in Kenya together with hormone replacement therapy. (35)

Age at initial diagnosis poses a major risk issue for the development of VTE. The number of new cases of VTE has been found to be typically highest in the first 6 -12 months after diagnosis. (36) It usually remains constant afterward. Studies have additionally indicated that the diagnosis of VTE in cancer is could be a prognosis of late-stage cancer disease. (30)(37)

The incidence of breast carcinoma is very extremely connected to the increasing age. Early-stage of menarche, late onset of menopause, a later age during the first gestation and low parity are reproductive system factors that can escalate the breast cancer risk. There is a rise in the danger of getting breast cancer by 3% for each 1-year delay in menopause (38) Family history is also another major factor that needs to be considered. It is estimated that nearly 25% of all breast cancer patients have a relative who has suffered from the same disease. Studies by Michelle *et al* indicated a case family history of carcinoma of the mammary glands

contended to be a crucial threat for the development of second primary breast cancer among ladies with a previous stage 0 breast cancer. (24)

In social aspects, the present-day lifestyles such as extreme alcohol consumption and intake of a lot of dietary fat can increase the risk of developing breast carcinoma. The estrogen receptor pathways can be triggered as a result elevate the levels of estrogen due to alcohol consumption. (38) While no strong association has been shown, various studies show that the risk of breast cancer is increased in females who drink and smoke. (39)

Obesity is a known risk factor that causes VTE in the general population. The other risk factors that cause mortality in breast cancer patients are very low physical activity and selected comorbidities. Co-morbidities that co-exist with breast malignancy are many. The commonest comorbidities associated with breast cancer are hypertension, Chronic Obstructive Pulmonary Disease (COPD), rheumatologic disease, and diabetes mellitus. (40)

Research by use of the Charlson Comorbidity Index shows that when the Charlson Comorbidity Index score (CCI) increases with an increase in the number of comorbidities, there is a decrease in survival. (41) Because of the comorbid conditions, the definitive treatment of breast cancer was not given so this may affect the treatment of breast cancer. (42) Low physical activity which is consistent with a sedentary lifestyle has been shown to be a higher risk of mortality. This is mainly seen in breast cancer patients with higher BMI. (43) It is because of this patient-related risk factors that the ASCO (American Society of Clinical Oncologists) recommends that Cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. (44) (40)

2.3.2 Tumor related factors as risk factors for the development of VTE amongst breast cancer patients

Tumor connected factors that can result into the development of VTE amongst breast cancer patients include where the tumor is located, the tumors histologic site, stage of the tumor and the tumor's grade. Higher proportions of VTE in patients with solid tumors has led to suggestions that the incidence of VTE is higher than that that is observed in the real-world setting. (9)

Additionally, the danger of venous thrombosis has been shown to be highest in the early few months after the diagnosis of breast cancer. Folks who are carriers of the factor V Leiden mutation and also who also had breast cancer had a higher risk as compared to individuals without cancer and factor V Leiden. Patients with breast cancer with distant metastases or in this case stage four breast cancer have a greater threat as compared to patients who had a lesser stage of metastasis. (45) (27)

2.3.3 Chemotherapy related factors as risk factors for the development of VTE amongst breast cancer patients

The main use of chemotherapy medicines is to eliminate cancer cells. With breast carcinoma, chemotherapy serves three major functions. These include adjuvant therapy that is utilized for stopping cancer from coming back after surgery and radiation. (46) Neo-adjuvant therapy is where chemotherapy is employed to scale down the size of a tumor before surgery. Finally, it can be used to eliminate malignant cells that have spread to the various parts of the body. (19) (37)

Women who go through drug therapy for cancer management have extremely high rates of VTE while undergoing cancer drug therapy and in the initial month after stopping of therapy. It, therefore, means that women who are exposed to more cycles of chemotherapy stand a higher chance of getting a VTE episode. The threat of occurrence of VTE remained to be great in the second month after finishing treatment. However, by the third month, the danger of VTE development had returned back to that before undergoing treatment. (27) The use of tamoxifen increased the risk of VTE to more than fivefold in the 3 months after starting therapy among females who treated with tamoxifen only. (27) Studies also show that women who were African American compared to white women appear to have the same risks of contralateral breast cancer and VTEs in response to tamoxifen treatment. (47)

Tamoxifen therapy increases the risk of DVT and PE. Women receiving this therapy are at approximately 2.5 times greater risk during the first 5 years after breast cancer surgery. However, it has been found that there is a decrease in the tamoxifen effect by duration of therapy, with the first 2 years after the initiation of therapy constituting the period of greatest

increased risk. Risk during the following 3 years has not been found to be substantially increased. (48)

The common chemotherapy drugs that are used to for the management of early breast cancer include anthracyclines and taxanes. (17) Anthracyclines are a group of drugs that includes adriamycin and epirubicin. The taxane group of drugs includes docetaxel and paclitaxel. These drugs can be found to be commonly used with others like 5 fluorouracil (5-FU), cyclophosphamide and carboplatin. Fluorinated pyrimidines like 5-FU, and capecitabine cause vasospasm, arterial also and venous blood coagulation. (49) Cisplatin which is commonly used together with dexamethasone to help prevent vomiting causes endothelial injury, Raynaud's phenomenon, and thrombosis. (50)

Some women could have the Human Epidermal Growth factor Receptor 2 (HER2) gene also known as the human epidermal growth factor receptor 2 (HER2). This factor mainly functions by promoting the growth of cancer cells. Women who have the HER2 gene can be given either emtansine, lapatinib, pertuzumab, or trastuzumab. (27)

Various other drugs that are used in the control of breast carcinoma are known to also cause VTE in breast cancer patients. L-asparaginase has been shown to change plasma levels of pro-coagulants and anti-coagulants Antithrombin III, protein C, and S. In addition, tamoxifens modifies blood levels of coagulation factors. (8)

Dexamethasone which is additionally used as an anti-emetic causes change in plasma levels of blood clotting factors. Factors that stimulate erythropoiesis tend to change plasma levels of blood clotting factors. Thalidomide and lenalidomide, are known to cause endothelial injury, and also alter plasma levels of clotting factor VIII, which is also known as the von Willebrand factor. (51)

2.4 Management of Venous Thromboembolism amongst breast cancer patients

VTE occurrence in cancer patients results from a combination of cancer-induced hypercoagulability, endothelial and vessel wall damage, and venous stasis. Management of cancer-associated VTE remains a challenge given limited trial data for many oral

anticoagulant medications. (52) The main reasons for VTE treatment are to avoid death and disease due to PE, avoid repeated VTE episodes and to avoid lasting VTE and PE complication like post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. (53)

Patients who are diagnosed with breast carcinoma are at danger of VTE due to the hyper-coagulable state that they are in. Diagnosis of DVT has proved to be a difficult case in resource-limited settings. The patient's history is essential in determining whether any VTE risk factors are present in the patient. The family history of VTE increases the likelihood of DVT. Acute shortness of breath or chest pain in the setting of concerning lower extremity findings for PE and it should raise concern for DVT and concurrent PE. In resource-limited settings, the diagnosis and resolution of the VTE episode can be determined by using the Homan's sign. A positive Homan's sign is usually indicated by pain in the calf on the dorsiflexion of the foot. This is thought to be associated with the presence of thrombosis. Clinical examination and the Homan's sign have low sensitivity and specificity in diagnosing DVT. However, both are essential and can be used in resource-limited settings.

Venous Thromboembolism Events can be determined by use of the Doppler in resourceful settings. It should be noted that anticoagulants are not recommended to improve survival in patients with cancer without VTE. Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies. (44)

However, the issuance of prophylaxis is not advised as it may lead to excessive bleeding of the patient. Consequently, the treatment of VTE in breast cancer is typically more complex because of high rates of recurring VTE together with a higher risk of hemorrhage if the patient is placed on treatment with anticoagulants. (52)

Various approaches have been used in the management of VTE in cancer patients. With various guidelines currently in place, the common ones being the American Society of Clinical Oncologists (ASCO) Guidelines and the National Comprehensive Cancer Network (NCCN) guidelines. The ASCO recommendations for the management of cancer patients tend to vary depending on the clinical situation of the patient. For in-patients, hospitalized

patients who have active malignancy with acute medical illness or reduced mobility are recommended to receive pharmacologic thrombo-prophylaxis in the absence of bleeding or other contraindications. However, hospitalized patients who may be having active malignancy without additional risk factors may be considered for pharmacologic thrombo-prophylaxis in the absence of bleeding or other contraindications. There is however inadequate data to support routine thrombo-prophylaxis in patients who have been admitted for minor procedures or a brief infusion of chemotherapy. (44)

ASCO doesn't recommend any routine pharmacologic thrombo-prophylaxis in cancer outpatients. However, based on limited data, clinicians are advised to consider LMWH prophylaxis only on a case-by-case basis in highly selected outpatients who have solid tumors and are receiving chemotherapy. Consideration of such case by case therapy should be conveyed through a discussion with the patient about the uncertainty concerning benefits and harms, as well as dose and duration of prophylaxis in this setting. (44)

While managing the underlying condition is fundamental to the management of VTE, various studies have come up with varying approaches to managing VTE. These include the use of plasma and anti-platelet agents including heparin, oral anticoagulants and fibrinolytic agents. (54) Some published works have indicated using LMWH as being superior to the use of unfractionated heparin. (55)

Low-molecular-weight heparin (LMHW) continues to be mainly preferred as an anti-coagulant of choice due to a number of reasons. It has been shown to be additional effective than warfarin at decreasing the threat of recurrent VTE in patients with DVT/PE and active cancer. (56) Even more importantly, studies have shown that LMWH has been shown to decrease the danger of bleeding in these patients with recent studies citing LMWH as having some antineoplastic effects and may even reduce cancer-related mortality hence being advantageous for utilization in the management of VTE in patients affected by cancer. (57)

For patients who have multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for low-risk patients and LMWH for high-risk patients. (44) This is because Thalidomide and lenalidomide induced endothelial injury

and their alteration of the plasma levels of the von Willebrand factor which is also known as clotting factor VIII,

As for perioperative patients, all patients with malignant disease undergoing major surgical intervention are to be considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or a high risk of bleeding with the procedure. The prophylaxis should be commenced preoperatively and mechanical methods may be added to pharmacologic thromboprophylaxis, but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding or high bleeding risk. A combination regimen of pharmacologic and mechanical prophylaxis may, however, be used to improve efficacy, especially in the highest-risk patients. (44) Pharmacologic thromboprophylaxis should still be continued for at least 7-10 days in all perioperative patients. Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors.

For treatment and secondary prophylaxis, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the cancer patient with newly diagnosed VTE who does not have any severe renal impairment. Renal impairment is defined as a creatinine clearance below 30 mL/min. In addition, if the anticoagulation is to be done for a longer duration, LMWH for at least 6 months is preferred due to improved efficacy over Vitamin K antagonists. Vitamin K antagonists are an acceptable alternative for long-term therapy if LMWH is not available.

ASCO recommends anticoagulation with LMWH or Vitamin K antagonist beyond the initial 6 months be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy. It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite maximal therapy with LMWH. For patients with central nervous system malignancies, anticoagulation is recommended for established VTE

as described for other patients with cancer. However, careful monitoring is necessary to limit the risk of hemorrhagic complications. ASCO advises that incidental PE and DVT should be treated in the same manner as symptomatic VTE.

It is, however, encouraging to note that there are a number of new oral and parenteral antithrombotic agents are currently under development which is likely to have a future application to patients with malignant disease. (44) The use of oral anti-coagulants which act directly on the clotting factor X and Xa has been found to be an attractive alternative in patients with cancer because they are administered in a fixed-dose and therefore do not require laboratory monitoring. (58)

On the evaluation of Direct Acting Oral Anti Coagulants (DOACs) for the prevention of VTE predominantly in patients undergoing orthopedic surgery, they were found to be effective and safe compared with LMWHs according to the surrogate outcome of postoperative venography. In some studies, it appears that rivaroxaban is actually superior in terms of the reduction of asymptomatic DVT. (59)

The lack of data that has been published on the benefits of VTE reduction through thrombo-prophylaxis versus the risks of bleeding has been highlighted as one of the reasons why guideline recommendations are not routinely followed by physicians. However, the International Initiative on Thrombosis and Cancer (ITAC) established to set guidelines on the management of VTE and thrombo-prophylaxis in cancer patients. The principal investigator intends to use these guidelines in his review of the management of VTE in breast cancer patients. (60)

The ITAC panel recommended initial treatment to be done in the first 10 days of anticoagulation with a strong recommendation (grade 1B) for the use of Low-molecular-weight heparin (LMWH) for the initial treatment of established VTE in patients with breast cancer. A once-daily regimen of LMWH was recommended unless a twice-daily regimen was required because of patient characteristics. This is to be maintained for 10 days to 3 months and long-term beyond 3 months. The guidelines recommend strongly recommend LMWH to be used for a minimum of 3 months to treat established VTE in patients with cancer. After 3 to 6 months, the guidelines recommend continuation or stopping the use of anticoagulation

therapy based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity. (60)

In case there is a recurrence of VTE, the guidelines indicate three options for management. The first is to increase the dose of LMWH by 20–25%, or switch the patient from VKA to LMWH in patients treated with VKA and finally, they recommend inferior vena cava filter insertion with continued anticoagulant therapy.

In the prophylaxis of venous thromboembolism (VTE) in breast cancer patients, the management was divided into surgical patients and medically treated patients. In surgical patients, the use of low-molecular-weight heparin (LMWH) once daily or the use of low-dose unfractionated heparin (UFH) three times per day was recommended to prevent postoperative VTE. Ideally, pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days after the surgical procedure.

In the prophylaxis of VTE in medically treated patients with cancer, the use of LMWH, UFH, or fondaparinux was recommended in patients with cancer and reduced mobility who were admitted to the hospital. The routine use of direct oral anticoagulants was however not recommended. (60)

However, further studies indicate better and more tolerant anti-coagulant agents like the factor Xa inhibitors and directly acting anticoagulants can be used. The use of factor Xa inhibitors which act directly on the clotting factor X and Xa are a better alternative. This is because the healthcare personnel can do a fixed-dose administration and as a result, and therefore do not require laboratory monitoring. (58) Studies by Bergqvist *et al* indicate that rivaroxaban is actually superior in terms of reduction of asymptomatic DVT. (59) The use of Direct-Acting Oral Anti Coagulants (DOACs) for the prevention of VTE predominantly in patients undergoing orthopedic surgery, was found to be safe and effective as compared to LMWHs. There was no documented evidence on the use of an anticoagulant for thrombo-prophylaxis amongst the breast cancer patients.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter strived to explain the study population, study area and the characteristics of the population. It also delved into the sampling methodology that was used, research instruments used and data collection techniques. The principal investigator also explained how the validity and reliability of the study were upheld. Finally, this chapter explains the data management methods that were used and finally the logistical and ethical considerations for the study.

3.2 Study design

The study adopted a cross-sectional study design. A cross-sectional study was preferred because it is more suitable to measure the prevalence of behavior or disease. This method was considered to be comparatively simple, inexpensive and enabled quick data collection within the given time frame. Moreover, this method was also considered valuable in the development of hypotheses for the future and further research. (61) . In addition, similar studies were conducted by Jihane *et al* with great success hence compelling the researcher to adopt the same design in this study. (34)

3.3 Study site

The study was conducted at Kenyatta National Hospital (KNH) in the oncology department. KNH is located in Nairobi County. The hospital is situated in the immediate west of Upper Hill in Nairobi, 3.5 kilometers from the central business district of Nairobi County along Hospital road (off Ngong Road). Kenyatta National Hospital has a capacity of 1800 beds and has over 6000 staff members. It covers an area of 45.7 hectares. The University of Nairobi Medical School and several government agencies are located on the campus. KNH has 51 wards, 22 out-patient clinics, 24 theaters (16 which are specialized) Accident and Emergency Department. Out of the total bed capacity of 1800, 209 beds are for the Private Wing. Of the 51 wards, 5 of these wards which are dedicated to the management of cancer. The inpatient

wards and outpatient department are run by a team of physicians, nurses, radiologists, pharmacists, physiotherapists and nutritionists amongst other cadres. KNH was chosen due to its ease of accessibility in addition to the collaboration between the University of Nairobi and KNH in academia and research. With KNH being the largest referral hospital in Kenya, with a fully-fledged cancer unit, where most of the breast cancer cases are referred to from other facilities hence it was easy to get a better representation and larger samples to be used for the study.

3.4 Target Population and study population

The target population was all patients who are aged 18 years and above and had been diagnosed with breast cancer and were on treatment for the same. The study participants were patients aged 18 years and above diagnosed with breast cancer at any age and undergoing treatment at KNH within the period from July 2018 to June 2019. Participants who met the inclusion criteria were incorporated in the study. When the appropriate participant's files had been identified, the principal investigator examined their records to asses for the exposures which were breast cancer and the outcome which was an episode of VTE.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

All breast cancer patients who are aged 18 years and above with no upper age limit who had been on treatment during the period from July 2018 to June 2019 were considered for the study. Breast cancer patients were patients who had been diagnosed and confirmed to have breast cancer by the use of a mammogram. (32)

3.5.2 Exclusion criteria

Patient who reported to have had a VTE prior to first cancer diagnosis were not considered for the study. Additionally, all patient files for patients with cognitive or mental impairment were not considered for the study as these conditions would limit activity and communication.

3.6 Sampling

3.6.1 Sample size determination

The size of the sample was determined by the use of the Cochran formula. The Cochran formula was used because it allows estimation of the ideal sample size with a desirable level of precision and desired confidence level.

$$n_0 = \frac{Z^2 pq}{e^2}$$

Where:

n_0 = sample size required for the study

z^2 = the standard normal deviate set at 95% CI (z = 1.96)

e = Margin of error/desired level of precision set at 5% = 0.05

p = the estimated prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital. With the focus being on VTE whose prevalence is unknown, then we'll consider p = 0.5

q = 1-p

Therefore substituting for the values,

$n_0 = \frac{1.96^2 * 0.5(1-0.5)}{0.05^2}$

n_0 = 384.16 ~ 385 patients

3.6.2 Sampling procedure

The researcher used simple random sampling on the patient files for patients with breast cancer in order to obtain a representative sample of the target population. Essentially, all the patient files that met the inclusion criteria had an equal chance of participating in the study.

The earliest recorded date in the cancer registry data was used to determine the date of a cancer diagnosis. The patient population list was obtained from the KNH health records information Office and oncology out-patient and in-patient registers. Data was collected during the clinic hours for outpatients on weekdays. The principal investigator would initially go through the files, screening the file using the eligibility criteria screening tool (Appendix I). For chemotherapy, events were frequently recorded as a series of day case or outpatient procedures. As a result, they were considered part of the same course of treatment when occurring within 28 days.

Thereafter, the researcher created a list of all the eligible patient's files. For ease of identification, the principal investigator immediately tagged the files which meet the inclusion criteria using random unique numbers. The tag remained in the file until completion of the study. To avoid duplicate sampling, the Principal investigator used random unique numbers that were different from the patient's file number. The list of random unique numbers were separately matched to the file number and stored for the de-identification of the patient's file number. Additionally retaining the tags in the files would have posed a challenge due to improper filing. In this regard, the principal investigator mitigated this by making it compulsory to assign the random unique numbers to each patient to avoid picking the file again. Data was then collected from the files at first file on contact basis in no particular order.

3.7 Research instruments

3.7.1 Eligibility screen form

This tool will have the study information, participant information, inclusion criteria, and exclusion criteria. This is to help determine eligibility of the participants for the study. (Appendix 1).

3.7.2 Data collection form

Data collection was done by the use of data collection forms to get information as per the laid out objectives. Data collection forms were used because the researcher considered them to be

fast and efficient to collect data in the given time frame. The earliest recorded date in the cancer registry data was used to determine the date of a cancer diagnosis. They contained biodata, socio-demographic, clinical information of the patient. Information on the height, weight, and BMI were obtained from the KNH Nutrition Care Process form 362. Information was collected on the patient characteristics, tumor-related characteristics like the type, stage of tumor and duration since first diagnosis. Data on the staging of the patients was obtained from the KNH Breast Multi-Disciplinary Team (MDT) form 507 and KNH staging form 505. Chemotherapy related factors like the number of cycles, platelet count and hemoglobin level were also collected from the patient files data inclusive of the lab profiles of the patients. Data on the duration of days hospitalized, if they had undergone any surgery or radiation was also sought. It was also attached to the validated Khorana risk assessment tool for the risk of VTE in breast cancer patients to get the risk of developing VTE in these breast cancer clients. (Appendix 2) (9)

3.8 Pre-testing and Pilot study

The acceptability of the methods that were used for data collection was pre-tested. The pre-testing was done amongst 7 eligible patients files in the oncology department KNH. The results from this pretesting gave insight on how clear and concise the tool can be used for the data collection within the given time frame. The questions were further simplified and refined for ease of use by the researcher. Notably, significant changes were made to the data collection tool upon pre-testing. Contamination was minimized as the pre-tested data collection tool was marked and not included in the final analysis.

3.9 Validity

Validity is a feature credited to the intention or estimation to what degree they imitate the established facts or the truth. Therefore it denotes the degree to which an instrument can measure what it sets to measure (62). Various data elements like the type of data, range of values, missing values, consistency and total cross-referencing were checked. The research instruments were issued to fellow peers, lecturers and supervisors for cross-checking and scrutiny. In addition, the Khorana risk assessment tool that was used is a validated and

approved tool for risk assessment. (14) The data collection tool was then tested in the pilot study and then necessary corrections made to ensure content validity. Data validation enabled the correction of incorrectly entered data into EMS or set up an error flag which was later followed up.

3.10 Reliability

Reliability may be defined as a measure of the extent to which a research instrument yields results or data which are consistent after repeated trials. (63) The principal investigator used Pearson's Product Moment formula to obtain the correlation coefficient so as to test the reliability of the instruments. (64) So as to make sure that there is a high degree of reliability of instruments in gathering data for this study, the principal investigator personally collected the data.

3.11 Data collection techniques

Data was collected from the 377 eligible files by use of data collection tools upon the relevant approval being obtained. The data collection tools had the patient's bio-data, socio-demographic and clinical profile data. Also attached was the Khorana risk assessment scale for the risk of developing VTE in breast cancer patients. Treatment schedules, prescriptions and medical records belonging to the patient were reviewed and data collected. The data collection forms were filled appropriately and any additional information that was obtained recorded by the principal investigator while ensuring confidentiality. The information obtained was received and organized for data management.

3.12 Variables and Definitions

3.12.1 Exposure terminology

Breast cancer was the exposure variable. Breast cancer patients were patients who have been diagnosed and confirmed to have breast cancer by the use of a mammogram for at least a year from the day of first diagnosis. The earliest recorded date in the cancer registry data was used to determine the date of a cancer diagnosis. The various exposure characteristics regarding

the files that fit the inclusion criteria about the patient characteristics, tumor, and chemotherapy-related factors were investigated.

3.12.2 Outcome status terminology

The outcome status terminology was used to describe the clinical outcome status resulting from having breast cancer for a year or more. This outcome was in the form of a VTE which was indicated as an event of Pulmonary Embolism or Deep Vein Thrombosis. (32)

3.13 Data management

3.13.1 Data processing

The data collection forms were checked for completeness, accuracy and internal consistency. Any data of doubtful quality were excluded from the study. However, any questions excluded because of incompleteness or inconsistency in the answers were discussed in the final report. Upon completion of filling the data collection forms, the data was verified and checked for any data entry mistakes and any mistakes or erroneous inputs corrected.

The data was then entered into dummy tables that were inputted in Microsoft Excel for Microsoft Windows XP 2010 upon completion of the filling of the data collection tools on a daily basis. The data was backed up every three days on a flash disk that was password protected for the sake of data confidentiality. After data entry, the data was cleaned and entered into STATA version 13.0.

3.13.2 Data quality control

Data control measures were implemented at every stage from data collection, data processing, data entry, analysis and interpretation of the data. Thorough appraisal and scrutiny data collection forms were done with well-defined procedures on data collection with strict application of procedures in regards to data quality control norms and practices. These practices included data quality assessment, data quality measurement, incorporating data quality into the functions and processes.

The data collection form was checked for completeness, accuracy, and consistency. During data entry, the data was checked for blank or missing values, out of range values and inconsistent responses. Data analysis was checked for inconsistencies during the interpretation of the results. The principal investigator also sought and got an independent review of the analytical results so as to help detect any data anomalies.

3.13.3 Data analysis

The data was entered into Microsoft Excel 2010 and analyzed using STATA version 13.0. Univariate analysis was done for descriptive statistics like age, weight, and BMI by using measures of central tendency like the mean, median and standard deviation and dispersion for numerical data and frequencies and proportions for categorical data. This was to help to establish the prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at KNH. This data was presented in the form of frequency tables, bar charts and pie charts as appropriate.

The investigator used the Khorona Risk assessment score for VTE in cancer patients. This score helped act as a predictor of future risk of venous thromboembolism in cancer patients initiating chemotherapy in the cancer clinic. The tool was used as it is a simple and validated tool for the prediction of future risk of venous thromboembolism. (32) Consent on the use of the tool was obtained from Khorana M.D Alok.

The risk factors associated with developing venous thromboembolism in patients with breast cancer was additionally analyzed by using inferential statistical analysis. The risk factors associated with developing venous thromboembolism in patients with breast cancer was additionally analyzed by using inferential statistical analysis. Bivariate analysis was conducted to determine associations between the predictors of the risk of development of a venous thromboembolic event and the sociodemographic characteristics, clinical characteristics and treatment characteristics using Fisher Exact test at 95% Confidence Interval (CI). Fisher Exact test was preferred due to the small prevalence of breast cancer and hence smaller cell sizes of <5 and a sample size of less than 1000. Values which had a $p \leq 0.05$

were considered statistically significant. A dummy table (Appendix 3) was used as a guide for the analysis.

3.14 Delimitations of the study

The study was conducted by using simple random sampling at the oncology clinic based at KNH. Patient files which meet the inclusion criteria were subjected to data collection.

3.15 Limitations of the study

Being a cross-sectional study, the study wasn't able to accurately establish the incident cases. The study collected more data on prevalence as compared to the incidence of VTE amongst breast cancer patients. Because of time and monetary limitations, the study period and sample size were also relatively smaller hence affecting the validity and generalizability of the study.

This study design is however prone to selection and information bias. Selection bias was countered by proper sampling methods. Information bias was minimized by use of a standard data collection tool, the use of objective units of measure, and using objective records where feasible rather than recall.

3.16 Ethical and logistical considerations

The permission to carry out the study was obtained from the Ethical Review Committee, University of Nairobi/KNH reference number P326/04/2019. (Appendix 4) On obtaining approval from UoN/KNH Ethical Review Committee to carry out the study, the institutional approval from KNH Department of Research and Programs was obtained. (Appendix 5)

The researcher applied beneficence in evaluating the potential danger of harm and any potential benefits that may be gotten by the participants, thoughtful to the rights and interests of participants, and reflected on the socio-cultural implications of the study that was undertaken. The principal researcher also hopes that breast cancer patients will benefit from the research. The researcher will strive to ensure confidentiality and the respondents' data findings will be used strictly for academic purposes.

Upon completion, the principal researcher placed all the data collection tools in a secure place under lock and key. The tools will be stored for a period of five years from the date of

publication of the study. Upon completion of the retention period, the data collection tools will be disposed of by the use of a paper shredder. Digital data if available will be destroyed by deleting or overwriting information. The researcher will, however, intend to adhere to any disposal procedure or protocol that will be in place by the UoN/KNH ethics committee at the end of the retention period.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter mainly dwells on the analysis of the data that was collected and presented in accordance with the already set out objectives. Data analysis for descriptive data was done and presented in the form of frequencies, proportions, and figures. Bivariate analysis was done to show the relationship between the predictor variables (Surgery, radiation, and chemotherapy-related factors) versus the outcome variable of VTE which was presented as either Deep Vein Thrombosis or Pulmonary Embolism.

4.2 Patient characteristics

A total of 377 breast cancer patients files were used in the study within the study period. There were 371 female and 6 male patient files involved in the study with a majority of them (98.4%) having ductal breast cancer. This is indicated in the Table 1 below.

Table 1: Breast cancer patient characteristics (gender, type of breast cancer)

Characteristic	Patients (n = 377)	
	No.	%
Gender		
Male	6	1.6
Female	371	98.4
Type of breast cancer		
Ductal	371	98.4
Lobular	6	371

A majority of the patients were aged 30-50 years with a relatively lesser population of participants aged below 30 years. Most of the patients had an ideal BMI of 18.5-24.9. This is illustrated in table 2.

Table 2: Breast cancer patient characteristics (Age, BMI)

Characteristic	Patients (n = 377)	
	No.	%
Age (years)		
<30	49	13
30-50	207	54.9
> 50	121	32.1
Body mass index (kg/m^2)		
Underweight (<18.5)	8	2.1
Ideal (18.5-24.9)	230	61
Overweight (25.0-29.9)	121	32.1
Obese (30.0-39.9)	18	4.8

A majority of the patients 156 (41.38%) were found to have stage 2 breast cancer and stage 3 breast cancer 115(30.5%) with comparatively fewer cases of stage 1 breast cancer 3 (0.8%). Additionally, 308 (81.7%) of the patient files indicated that the patients had at least one form of comorbidity. This is indicated in figure 2 below.

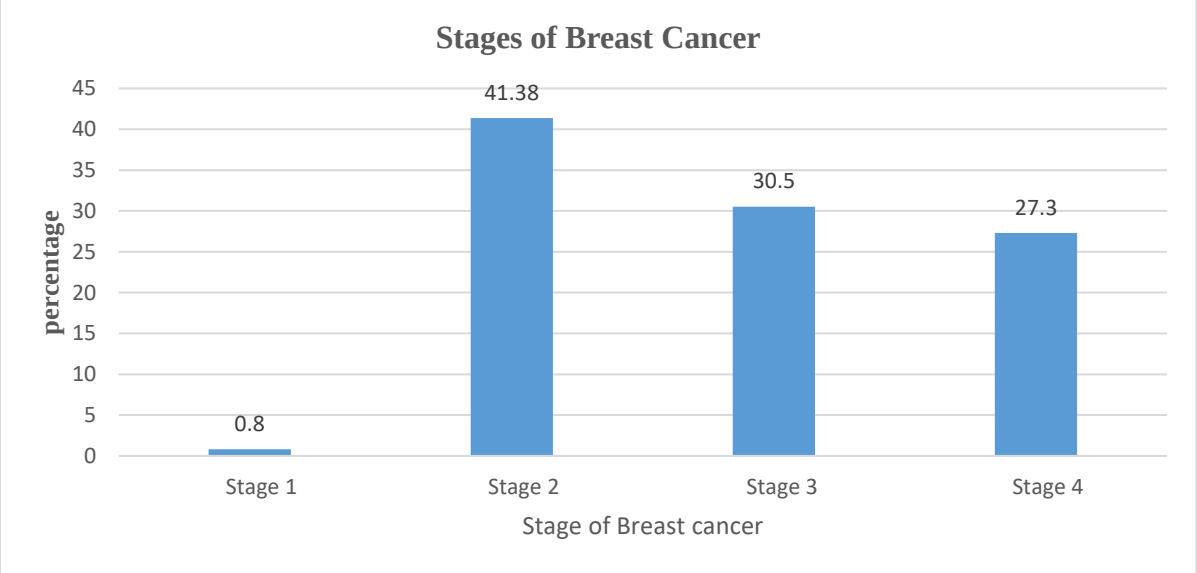

Figure 2: prevalence of breast cancer by stage

Most of the patients underwent breast cancer management in the form of surgery, radiotherapy, and chemotherapy at one stage or the other. Most of the patients underwent surgery at some point after a cancer diagnosis, 98.4% went through chemotherapy, and 49.07% were prescribed radiation therapy.

Surgery is one of the principal strategies in the management of breast cancer. In relation to this, surgery in the form of a mastectomy occurred on average 5.7 months (SD 3.4) after the initial cancer diagnosis. On the other hand, chemotherapy was initiated at an average of 2.2 months (SD 1.6) after surgery while 12.8 % received neo-adjuvant chemotherapy. This is illustrated in **Table 3** below.

Table 3: Characteristics of patients with breast cancer (Surgery, Radiotherapy, and Chemotherapy)

Surgery	**No**	**%**
Yes	326	86.47
No	51	13.53
Chemotherapy		
Yes	371	98.41
No	6	1.59
Radiotherapy		
No	192	50.93
Yes	185	49.07

4.3 Prevalence of VTE amongst breast cancer patients in Kenyatta National Hospital

VTE was observed in 10 (2.65%) of the patients from the total participant's files which were used in the study. Of the patients who had VTE episodes, 30% had a pulmonary embolism, 20% had Deep vein thrombosis of the upper extremities while the remaining 50 % developed deep vein thrombosis of the lower extremities as shown in **figure 3** below.

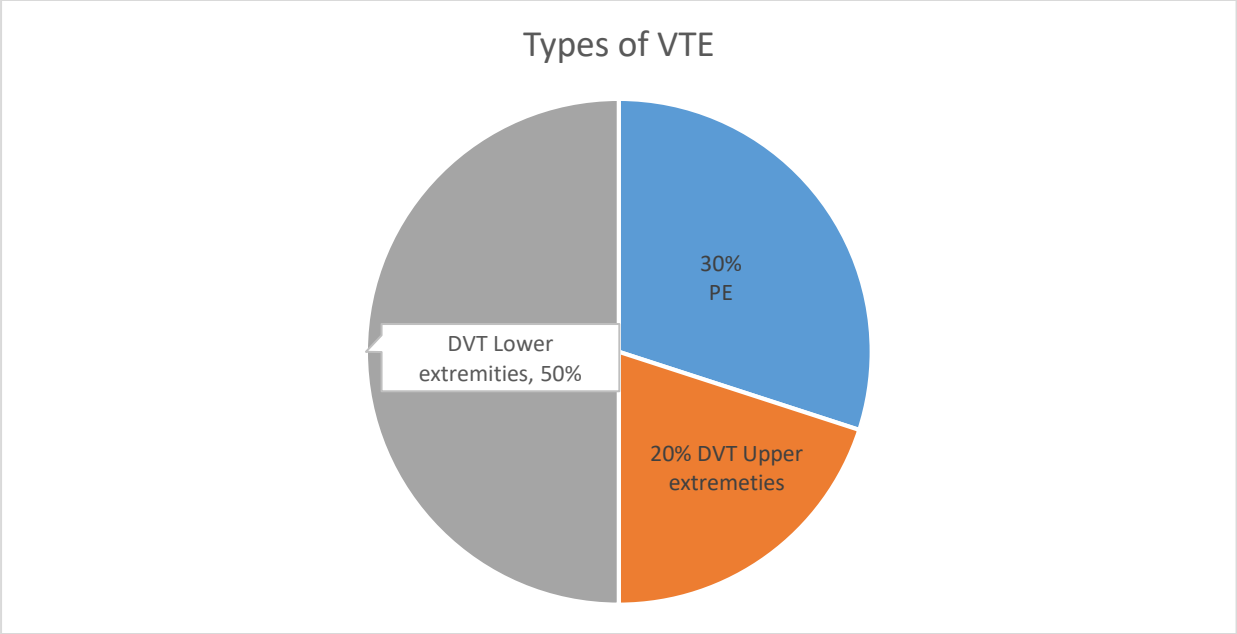

Figure 3: Types of VTE

By using the Khorana risk assessment scale, the patients were categorized as low risk, intermediate risk and high risk of developing a VTE event based on the score obtained. Most of the patients 298 (79.05%) were found to have an intermediate risk of developing a VTE event while 71 (18.8%) and 8 (2.12%) had low risk and a high risk of developing VTE respectively as shown in **Table 4** below.

Table 4: Risk of developing VTE

Score	Frequency	%
Low risk	71	18.8
Intermediate risk	298	79.1
High risk	8	2.1

The rate of VTE occurrence in breast cancer patients increased or decreased depending on various factors like the stage of cancer, age, presence of comorbidities, BMI and exposure to

radiation therapy, chemotherapy or surgery. 3.07 % and 4.32% of the participants who had more than one treatment modality of either surgery or radiotherapy developed VTE events respectively. In addition to that, all the patients who developed VTE had undergone some form of chemotherapy. This is illustrated in **Table 5** below.

Table 5: Prevalence of VTE in surgery, chemotherapy, and Radiotherapy breast cancer patients.

Characteristic	Patients (n = 377)		Patients with VTE (n = 10)	
	No.	**%**	**No.**	**%**
Surgery				
Yes	326	86.5	9	90
No	51	13.5	1	10
Chemotherapy				
Yes	371	98.4	10	100
No	6	1.6	0	
Radiotherapy				
No	192	50.9	3	30
Yes	185	49.1	7	70

Most of the patient files indicated that most of the patients 99.2% presented with stage 2, 3 and 4 breast cancer. Of the total patients with stage 2 breast cancer, 0.641% presented with VTE while stage 3 breast cancer had 1.74% VTE cases. Stage 4 had the largest number of VTE cases which was represented by 6.8% of all the stage 4 breast cancer cases as shown in **table 6** below.

Table 6: prevalence of VTE by Stage of Cancer

Characteristic	Patients (n = 377)		Patients with VTE (n = 10)	
	No.	%	No.	%
Cancer stage				
Stage 1	3	0.8	0	0
Stage 2	156	41.4	1	10
Stage 3	115	30.5	2	20
Stage 4	103	27.3	7	70

Most of the patients (50%) that had VTE were aged 30-50 years while 20% and 30% of the patients that had VTE were aged less than 30 years and more than 50 years respectively. In addition to that, all the patient files used in the study indicated that all the patients who had VTE had ductal type of breast cancer. This is illustrated in **table 7** below.

Table 7: prevalence of breast cancer by age and type

Characteristic	Patients (n = 377)		Patients with VTE (n = 10)	
	No.	%	No.	%
Age (years)				
<30	49	13	2	20%
30-50	207	54.9	5	50%
> 50	121	32.1	3	30%
Type of breast cancer				
Ductal	371	98.4	10	100%
Lobular	6	371	0	0%

Most of the patient files indicated most of the VTE patients to be overweight (50%) or obese (50%) with a BMI of 25-29.9 and 30-39.9 respectively. Additionally, all the patients who had

VTE had comorbidity with 80 % having more than one comorbidity. This is illustrated in **table 8** below.

Table 8: prevalence of VTE by BMI and number of comorbidities

Characteristic	Patients (n = 377)		Patients with VTE (n = 10)	
	No.	%	No.	%
Body mass index (kg/m^2)				
Underweight (<18.5)	8	2.1	0	
Ideal (18.5-24.9)	230	61	0	
Overweight (25.0-29.9)	121	32.1	5	50%
Obese (30.0-39.9)	18	4.8	5	50%
Presence of Comorbidity				
Yes	69	18.3	10	100%
No	308	81.7	0	
Number of comorbidities				
1	22	5.8%	2	20%
2	31	8.2%	8	80%
> 2	18	4.8%	0	

4.4 Association between Participants' characteristics and risk of developing VTE

The bivariate analysis was carried out to find out the association between the risk of developing VTE with the various predictor variables such as social demographic characteristics, clinical characteristics and the treatment approaches that were used in the management of VTE among the study patients.

4.4.1 Association between sociodemographic characteristics and risk of developing VTE

The bivariate analysis was carried out to compare the risk of developing a VTE with social demographic characteristics among the study patients by using Fischer's Exact test as seen in the table below. Age was found to be a statistically significant risk factor for developing VTE (p= <0.001) with most of the patients aged 30-50 years (54.9%) with an intermediate (46.7%, n=377) to high risk (1.3%, n=377) of developing VTE. The other socio-demographic characteristics of BMI and gender were not found to be statistically significant with p- values of 0.41 and 0.2 respectively. The findings are summarized in **Table 9** below.

Table 9: Association between sociodemographic characteristics and risk of developing VTE

		VTE Risk			P-values
Age(years)		**Low VTE risk**	**Intermediate VTE risk**	**High VTE risk**	
	<30	5	44	0	
	30-50	26	176	5	**<0.001***
	>50	40	78	3	
BMI					
	< 18.5	3	5	0	
	18.5-24.9	47	176	7	0.41
	25-29.9	19	101	1	
	>30	2	16	0	
Gender	Male	3	3	0	0.2
	Female	68	295	8	

*Statistically significant result

4.4.2 Association between clinical characteristics and risk of developing VTE

4.4.2.1 Association between tumor-related factors and risk of developing VTE.

Most of the patients (98.4%) had ductal breast cancer with the association between the kind of breast cancer and the risk of developing VTE being statistically significant (p=0.024). However, the stage of breast cancer was not found to be statistically significant (p=0.23). The analysis was carried out by use of the Fisher exact test. This is illustrated in **Table 10** below.

Table 10: Association between tumor-related factors and risk of developing VTE.

Variable	**VTE Risk**			**P-values**
Kind of breast cancer	**Low**	**Intermediate**	**High**	
Ductal	67	296	8	**0.024***
Lobular	4	2	0	
Stage of breast cancer				
Stage I	1	2	0	
Stage II	34	118	4	0.23
Stage III	19	96	0	
Stage IV	17	82	4	

*Statistically significant result

4.4.2.2 Association between duration since diagnosis, presence of comorbidities and number of comorbidities and risk of developing VTE.

There was a statistically significant association (p=<0.001) between the duration since the first diagnosis of breast cancer and the risk of VTE with most of the patients (46.7%) having been diagnosed more than 6 months prior to treatment.

Additionally, the presence of comorbidities and number of comorbidities were found to be a statistically significant risk of developing VTE at p=<0.001 and p=0.002 respectively. The analysis was carried out by use of the Fisher exact test. This is illustrated in **Table 11** below.

Table 11: Association between duration at first diagnosis and treatment, presence of comorbidities and number of comorbidities and risk of developing VTE.

Variable	VTE Risk			P-values
Duration between diagnosis and treatment	**Low**	**Intermediate**	**High**	
<3 months	28	51	0	
3-6 months	30	92	0	**<0.001***
>6 months	13	155	8	
Presence of comorbidities				
Yes	13	49	7	**<0.001***
No	58	249	1	
Number of comorbidities				
1	8	11	3	
2	3	28	0	**0.002***
3	2	12	4	
3-6 months	0	4	1	0.99
>6 months	0	2	0	

*Statistically significant result

4.4.3 Association between breast cancer treatment approaches and risk of developing VTE

4.4.3.1 Association between surgery and risk of developing VTE

There was a statistically significant association between the patients having surgery in the last one year and the risk of developing a VTE event (p=<0.001). Additionally, the duration it took to do the surgery after diagnosis was also found to have a statistically significant association with the risk of developing a VTE event. (p=<0.001). However, the duration it took to develop a VTE event after surgery did not have a significant influence on the risk of

developing a VTE event. (p=<0.378). The analysis was carried out by use of the Fisher exact test. This is illustrated in **table 12.**

Table 12: Association between surgery and risk of developing VTE

Variable	**VTE Risk**			**P-values**
Patient who had surgery in the last year	**Low**	**Intermediate**	**High**	
No	24	27	0	**<0.001***
Yes	47	271	8	
How long ago was the surgery done				
<3 months	29	75	1	
3-6 months	29	89	0	**<0.001***
>6 months	13	134	7	
Duration to development of VTE after surgery				
<3 months	1	1	0	
3-6 months	0	3	1	0.378
>6 months	0	4	0	

*Statistically significant result

4.4.3.2 Association between chemotherapy and the risk of developing VTE

The duration it took to initiation of chemotherapy since diagnosis was found to have a statistically significant association with the risk of developing a VTE event (p=0.012). The number of chemotherapy cycles was also found to have a statistically significant association with the risk of developing a VTE event (p=<0.001). The association between the risk of developing a VTE and if the patient was on chemotherapy was not found to be statistically significant (p=0.2). In addition, the association between the duration it took to develop a VTE

after chemotherapy and the risk of developing a VTE was also not found to be statistically significant (p=0.99). The analysis was carried out by use of the Fisher exact test. This is illustrated in **Table 13** below.

Table 13: Association between chemotherapy and the risk of developing VTE

Variable	**VTE Risk**			**P-values**
Patient on chemotherapy	**Low**	**Intermediate**	**High**	
No	21	170	1	0.2
Yes	50	128	7	
Duration to initiation of chemo since diagnosis				
<3 months	38	200	7	
3-6 months	33	84	1	**0.012***
>6 months	0	14	0	
Number of chemotherapy cycles				
< 3 cycles	40	60	0	
3-6 cycles	28	142	1	**<0.001***
> 6 cycles	0	93	7	
Duration of development of VTE after chemo				
<3 months	1	3	1	
3-6 months	0	2	0	0.99
>6 months	0	3	0	

*Statistically significant result

4.4.3.3 Association between radiotherapy and risk of developing VTE

There was a statistically significant association between the use of radiotherapy and the risk of developing a VTE (p=<0.001). The duration it took to initiation of radiotherapy since

diagnosis was also found to have a statistically significant association to the risk of developing a VTE event (p=<0.001).). In addition, the association between the duration it took to develop a VTE after radiotherapy and the risk of developing a VTE was also not found to be statistically significant (p=0.99) as illustrated in **Table 14** below.

Table 14: Association between radiotherapy and the risk of developing VTE

Variable	**VTE Risk**			**P-values**
	Low	**Intermediate**	**High**	
Patients on radiotherapy				
No	21	170	1	**<0.001***
Yes	50	128	7	
How long ago after radiotherapy				
<3 months	20	36	0	
3-6 months	32	50	0	**<0.001***
>6 months	0	42	7	
Duration to development of VTE after radiotherapy				
<3 months	0	1	0	
3-6 months	0	4	1	0.99
>6 months	0	2	0	

*Statistically significant result

4.5 Independent predictors of the risk of developing VTE in Breast cancer patients

Bivariate and multivariate logistic regression analysis was performed to determine the independent predictors of the risk of developing VTE.In the bivariate model, the characteristics that were found to be predictors included the number of chemotherapy cycles (COR=5.03; CI= 3.13-8.06; p=0.001). Those who went through more than 3 chemotherapy cycles were 5.03 times likely to have a VTE event compared to those who went through less

than 3 chemotherapy cycles. This prediction became clearer on multivariate analysis having controlled for the confounding variables as indicated in table 17. (AOR=8.6; CI=3.38-21.98; p=0.001).

Also, radiotherapy was also found to be a predictor of the risk of VTE (COR= 0.33; CI=0.19-0.58; p=0.001). Patients who had radiotherapy were 0.33 times likely to have a VTE event compared to those who didn't. This prediction was made more apparent when doing multivariate analysis. (AOR=0.09; CI=0.03-0.24; p=0.001). Additionally, age acted as a predictor of the risk of VTE (COR=0.37; CI=0.24-0.58; p=0.001). Patients who were aged were 0.37 times likely to have a VTE event compared to those who were of a lesser age. This prediction was strengthened on doing multivariate analysis. (AOR=0.47; CI=0.24-0.94; p=0.032).

The number of months since breast cancer was diagnosed also found to be a predictor of the risk of VTE (COR=1.38; CI=1.23-1.55; p=0.001). Patients who were diagnosed with breast cancer in more than 3 months before receiving treatment were 1.38 times likely to have a VTE event as compared to those who were diagnosed in less than 3 months before receiving treatment. This prediction was made to be more apparent in multivariate analysis. (AOR= 1.64; CI=1.1-2.44; p= 0.015).

Finally, patients who had surgery done in the last one year were 5.28 times likely to have a VTE event compared to those who didn't. (COR=5.28; CI=2.81-9.91; p=0.001). This relationship was made stronger on doing multivariate analysis (AOR= 0.68; CI=0.48-0.98; p=0.04).

The type of breast cancer (COR=0.11; CI=0.02-0.61; p=0.012), surgery conducted in the last one year (COR=5.28; CI=2.81-9.91; p=0.001) and the number of months since the last chemotherapy session (COR=1.78; CI=1.16-2.73; p=0.008) had strong associations while doing the bivariate analysis.

However, these associations were lost while doing the multivariate analysis by use of the Fisher exact test for type of breast cancer, surgery being done in the last one year and the number of months since the last chemotherapy session. The results for the bivariate and multivariate analysis that was done are as summarized in **Table 15**.

Table 15: Independent predictors of the risk of developing VTE in Breast cancer patients

	Variables	Bivariate		Multivariate	
		COR (95% CI)	**p-value**	**AOR (95% CI)**	**p-value**
1.	No. of chemotherapy cycles	5.03(3.13-8.06)	<0.001	8.6(3.38-21.98)	**<0.001***
2.	Patient on radiotherapy	0.33(0.19-0.58)	<0.001	0.09(0.03-0.24)	**<0.001***
3.	Age	0.37(0.24-0.58)	<0.001	0.47(0.24-0.94)	**0.032***
4.	Types of breast cancer	0.11(0.02-0.61)	0.012	0.16(0.01-1.82)	0.14
5.	Months since breast ca diagnosis	1.38(1.23-1.55)	<0.001	1.64(1.1-2.44)	**0.015***
6.	Months since surgery was done	1.27(1.16-1.38)	<0.001	0.68(0.48-0.98)	**0.04***
7.	Surgery done in the last one year	5.28(2.81-9.91)	<0.001	2.2(0.54- 8.80)	0.266
8.	Months since the last chemo	1.78(1.16-2.73)	0.008	0.75(0.40-1.41)	0.381

COR=Crude Odds Ratio AOR=Adjusted Odds Ratio

CI=confidence interval * Statistically significant result

4.6 Methods used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Of the patients who were involved in the study, 306 (81.17 %) were found to have an intermediate to high risk of developing a VTE event. Of the total study participants, VTE was observed in 10 (2.65%) of the patients from the total participant's files which were used in the study. Of these patients who had VTE episodes, pulmonary embolism, deep vein thrombosis of the upper extremities and deep vein thrombosis of the lower extremities were manifested in 30%, 20% and 50% of the patients respectively.

Of the patients that had a VTE event, 9 (90%) were managed by using low molecular weight heparin, 8(80%) were managed by use of Warfarin and 8(80%) were managed by using a

combination of the two agents. Only 2 of the patients were managed by using unfractionated heparin. None of the patients was put Oral factor Xa inhibitor or any other anti-coagulant drug.

In regards to the long term management, most of the patients 9(90%) were placed on Low Molecular Weight Heparin, and 7(70%) were placed on aspirin. 7(70%) were placed on both LMWH and aspirin as shown in **Table 18** below. There was however missing data on the long term management of one of the patients who had VTE.

Table 3; Methods used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Initial management of VTE		
LMWH	**Frequency(n=377)**	**%**
No	368	97.61
Yes	9	2.39
Warfarin		
No	369	97.88
Yes	8	2.12
Unfractionated Heparin		
No	368	99.46
Yes	2	0.54
Long term management		
LMWH		
No	368	97.61
Yes	9	2.39
Aspirin		
No	369	98.1
Yes	7	1.9

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses key findings of the study within the context of existing research literature. The initial part of this section describes the study participants and the comparison of these characteristics with other similar studies. This is followed by a comparison of the results with other similar studies that have been conducted. Conclusions and recommendations for policy, practice and further research have been highlighted based on key findings from the research study.

5.2 Discussion

Most of the patient files (98.4%) that were used in the study were for women as opposed to men. This may be attributed to the fact that breast cancer is the top cancer in women globally (10). In addition, because of the presence of estrogen in females, breast cancer is more prevalent in females than in males leading to an increase in female screening for breast cancer as opposed to men. (29) Subsequently, breast cancer has become a burden in developing countries due to breast cancer-associated mortalities and morbidities which mainly affect women. (11)

The number of patients who were found to have VTE events was found to be 10 (2.65%). This number was higher and found to be inconsistent with other studies which had been done to determine the prevalence of VTE amongst breast cancer patients by Khorana *et al* in America and additionally, in our region by Mutebi in South Aftrica which determined a prevalence of 1.8% and a mortality rate of 4% (28) (11)

It was also noted that most of the patients (87%) were aged 30 years and above. Age was found to be a significant predictor of the risk of the development of VTE with most of the patients aged 30-50 years. The patients in this age group had an intermediate to high risk of developing VTE. This prediction was further strengthened on doing multivariate analysis. In addition, studies on the risk factors and prevention of breast cancer by Sun Y-S have indicated that age-related factors like an early stage of menarche, late onset of menopause, a late age

during the first gestation and low parity are age related reproductive system factors that can escalate the breast cancer risk. (38). This was also consistent with studies by Cumber *et al* which indicated age as a risk factor for the development of breast cancer. (5)

The other socio-demographic characteristics of BMI and gender were not found to be statistically significant risk factors for the development of VTE. This was however contrary to studies done which indicated that low physical activity has been shown to be a higher risk of mortality which is mainly seen in female breast cancer patients with higher BMI. (43)

While only 18.3% of the patients had at least one comorbidity, the presence of comorbidities and the number of comorbidities were found to be a statistically significant risk of developing VTE. This association was similar to other studies that indicated the presence of comorbidities to be a risk factor for the development of VTE. (42). The type of breast cancer was also found to be associated with a risk for developing VTE with a majority of the patient files being for patients (98.4%) who had ductal breast cancer. This was comparable with studies by Key *et al*. (22).

The stage of breast cancer was not found to be statistically significant to the risk of developing an episode of VTE. This was however contrary to studies done which indicated that later stages of breast cancer were risk factors for the development of VTE. (45). It was nevertheless also noted during data collection that the staging of breast cancer was either missing, incomplete or in some cases not uniform in the KNH Breast Multi-Disciplinary Team (MDT) form 507 and KNH staging form 505.

Consequently, most of these files were omitted from the study. An additional point to note was that although the stage of breast cancer was not found to be a statistically significant predictor of the risk of developing an episode of VTE, the presence of regional lymph nodes and distant metastases were found to be associated with a risk of VTE in the study.

In addition, with most of the patients (46.7%) having been diagnosed more than 6 months prior to treatment, the study found that there was a statistically significant association between the duration since the first diagnosis of breast cancer and the risk of VTE. This was consistent with studies that were done by Cronin *et al* (36) in Denmark and Khorana *et al* (3).

With surgery being one of the foremost treatment approaches for breast cancer, the study found that there was a statistically significant association between the patients having surgery in the last one year and the risk of developing a VTE event. Additionally, the duration it took to do the surgery after diagnosis was also found to have a statistically significant association with the risk of developing a VTE event.

Patients who had surgery done in the last one year were 5.28 times likely to have a VTE event compared to those who didn't with this relationship made stronger on doing multivariate analysis. Similarities on this were drawn from studies done by Elyamany *et al* in Saudia Arabia on cancer-associated thrombosis. (13)

The duration it took to initiation of chemotherapy since diagnosis and the number of chemotherapy cycles were also found to have a statistically significant association to the risk of developing a VTE event. This prediction became clearer on multivariate analysis on the duration it took to initiation of chemotherapy since diagnosis. This was consistent with studies done on a Danish population by Hernandez *et al* on tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism. (48), another on African American women by Worta *et al* (47) and by Walker *et al* which was done on an English population recently. (65)

There was a statistically significant association between the use of radiotherapy and the risk of developing a VTE event. The duration taken to initiation of radiotherapy since diagnosis was also found to have a statistically significant association with the risk of developing a VTE event. This prediction was made more apparent when doing multivariate analysis. A point to note was that these findings were consistent with the insight that was obtained from the NCCN guidelines on Breast Cancer, Version 3.2018. (17)

Warfarin and LMWH were commonly used for the management of VTE as depicted by 8(80%) of the patients who were managed by using a combination of the two agents. However, both these agents have their downsides and should be used with caution. Namely, LMWH can cause transient thrombocytopenia in 25% of the patients during the first 5 days of treatment. With breast cancer patients being in a hyper-coagulable state, there is also the risk of hemorrhage. Warfarin, on the other hand, has been shown to have a narrow therapeutic

index and it is a common drug causing many drug-drug interactions. This is especially detrimental for breast cancer patients who receive many drugs for their therapy. (59)

The long term management of VTE amongst the breast cancer patients was mainly done by use of LMWH 9(90%) which conforms to the recommended ITAC guidelines. However, the use of aspirin 7(70%) while not contraindicated was found to add little value to the management of VTE once the patient was treated using LMWH. It should be noted however that most of these patients had other comorbidities which maybe were being managed using the aspirin. (60)

5.3 Summary and Conclusions

The results of this study indicated that there is a high prevalence of VTE events amongst patients that are attending the breast cancer clinic at KNH. There exists several predictors of the risk factors for the development of VTE were identified in the study. This included the number of chemotherapy cycles, age of the breast cancer patient, use of radiotherapy as a treatment approach, the number of months since breast cancer was first diagnosed and finally management by surgery in the last one year. There is, therefore, a need for strong measures for the prophylaxis and management of VTE amongst breast cancer patients.

5.4 Study Strengths and Weaknesses

This was the first study of its kind that was conducted in Kenyatta National Hospital that attempted to establish the prevalence, risk factors, and management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital. The study managed to identify social demographic characteristics, clinical characteristics, and treatment approaches associated with the risk of developing a VTE event. The study also managed to identify statistically significant associations between the risk of development of a VTE and a number of factors. These factors included the number of chemotherapy cycles, age of the breast cancer patient, use of radiotherapy as a treatment approach, the number of months since breast cancer was first diagnosed and finally management by surgery in the last one year.

The principal investigator used the validated Khorana risk assessment scale for this study. However, while the principal investigator found the scale easy to use, it also had its own short fall. The main shortfall was the use of the scale for pre-chemotherapy and pre-surgery. This leaves a gap of assessing patients that are already on chemotherapy.

The study that was conducted was a cross-sectional study. As a result, the study wasn't able to accurately establish the number of incident cases. Consequently, the study collected more data on prevalence as compared to the incidence of VTE amongst breast cancer patients.

In addition, the study was also prone to measurement bias/ investigator bias because the Principal Investigator relied on blood levels of leucocytes, platelets, and hemoglobin which were done in different laboratories in different times. Because of time and monetary limitations, the study period and sample size were also relatively smaller hence affecting the validity and generalizability of the study.

5.5 Recommendations

5.5.2 Recommendations for Further Research

All radiation, chemotherapy and surgical breast cancer patients who have a high risk of VTE should be placed on prophylaxis by using Low Molecular Weight Heparin.This was a cross-sectional study and therefore, interventional studies are important to establish the risk factors and management strategies for VTE in breast cancer patients.

5.5.1 Recommendations for Policy and Practice

Future research should focus on the development of similar easy to use risk assessment models which will help identify specific women with breast cancer for whom the benefits of prophylactic intervention may be recommended. Once such a model is developed, or the Khorana scale is adopted, policy guidelines should made to be used to educate the breast cancer patients about the warning signs and symptoms of VTE including DVT and PE. Additionally, modifiable risk factors for the development of a VTE like BMI should be identified early and adequately managed.

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APPENDIX 1: ELIGIBILITY SCREENING FORM

All patient files were screened to determine if they meet the eligibility criteria in accordance with the inclusion and exclusion criteria detailed as follows.

1. **Study information**

Title	**Prevalence, Risk Factors And Management Of Venous thromboembolism Amongst Patients Undergoing Breast Cancer Treatment At Kenyatta National Hospital**
KNH/UoN/ERC Protocol number	
Investigator	**Dr. Orangi Gavin Ongesa**

2. **Participant information**

Participant ID:	
Gender: Male ☐	Female ☐

3. **Inclusion Criteria**

Inclusion Criteria	**Yes**	No
Is the patient diagnosed with breast cancer?		
Is the patient aged 18 years and above?		
Is the patient on treatment for breast cancer?		

4. **Exclusion criteria**

Exclusion criteria	**Yes**	**No**
Has the patient reported to have had a VTE prior to a first cancer diagnosis?		
Is the patient diagnosed and being treated for breast cancer within the study period?		

5. **Eligibility statement**

The participant is Eligible ☐ /Not eligible for the study. ☐

APPENDIX 2: DATA COLLECTION TOOL

A. BIODATA

1.	Patient code	
2.	Name / Initials	
3.	Physical address/ Contact	
4.	Date of study	

B. SOCIAL DEMOGRAPHIC CHARACTERISTICS

1. Age (years) ☐
2. Weight (kgs) ☐
3. Height(meters) ☐
4. BMI (kg/m^2) ☐
5. Gender: Male ☐ Female ☐

C: Prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

The following questions were used to establish the prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

6. What is the kind of breast cancer does the patient have?

1. Ductal ☐ 2. Lobular ☐ 3. Other ☐

7. What is the TNM stage of the cancer? (Tick the appropriate section)

Primary Tumor		Regional lymph nodes		Distant metastases	
TX	1	NX	1	M0	1
T0	2	N0	2	M1	2
Tis	3	N1	3	unknown	3
T1	4	N2	4		
T2	5	N3	5		
T3	6	unknown	6		
T4	7				
unknown	8				

8. What is the stage of breast cancer?

I ☐ II ☐ III ☐ IV ☐

9. How many months ago was the patient was first diagnosed with Breast cancer?

Duration (months) ☐

10. a) Has the patient had surgery in the last year?

Yes ☐ No ☐

b) If yes, how long ago (months) ☐

11. Is the patient on chemotherapy?

Yes ☐ No ☐

If yes, how long many months since surgery was chemotherapy initiated? ☐

12. Has the patient had radiation therapy in the last year?

Yes ☐ No ☐

If yes, how long ago (months) ☐

13. How many cycles of chemotherapy has the patient been through? ☐

14. How many months since the last chemotherapy session? ☐

15. (a) Does the patient have any comorbidities?

Yes ☐ No ☐

(b) If yes, kindly indicate how many: ☐

16. (a) Did the patient have any venous thromboembolism?

Yes ☐ No ☐

(b) If yes, which type of venous thromboembolism

Venous thromboembolism type	Code
Pulmonary embolism	1
Deep vein thrombosis(Upper extremities)	2
Deep vein thrombosis (Lower extremities)	3
Other	4

17. If yes, how long ago in months did it take to develop VTE after

code		No. of months
1	After Surgery	
2	After Chemotherapy initiation	
3	After Radiotherapy initiation	
4	After Hospitalization	

D: Risk factors associated with developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital.

The following questions were used to evaluate the risk factors associated with developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital.

Adopted from the Khorana Predictive risk model for chemotherapy associated-VTE

	Patient characteristic	**Risk score**	Code
18	Site of cancer (Breast)		
19	Stage of cancer		
	Pre-chemotherapy platelet count ☐ less than 350×10^9/L		1
	☐ more than 350×10^9/L		2
	Hemoglobin level ☐ less than 100g/L		1
	☐ more than 100g/L		2
	Pre-chemotherapy leucocyte count ☐ less than 11×10^9/L		1
	☐ more than 11×10^9/L		2
23	Number of chemotherapy cycles 1 ☐ 2 ☐ 3 ☐ > 3 ☐		

E: Methods used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

The following questions were used to identify the methods used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Initial Management		
S.no	**Drug**	**CODE**
24	Low Molecular Weight Heparin	1
25	Warfarin	2
26	Unfractionated heparin	3
27	Other	4
Long Term management		
S.no	**Drug**	**Code**
28	Low Molecular Weight Heparin	1
29	Aspirin	2
30	Warfarin	3
31	Other	4

APPENDIX 3: DUMMY TABLES

Table 4: **Social demographic characteristics**

Sno.	**Characteristic**	**Mean (sd)**	**Median[IQR]**
1	Age		
2	Weight		
3	Height		
4	BMI		
	Characteristic	**n %**	
5	Gender		

Table 5: Prevalence of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Sno.	**Characteristic**									
6	Month since the patient was first diagnosed with Breast cancer									
	< 3 months		4 -6months		7-9 months		10-12 months		> 12 months	
	N	%	n	%	n	%	n	%	N	%
7	Cycles of chemotherapy									
	N						%			
8	Patient's stage of breast cancer									
	0		1		2		3		4	
	N	%	n	%	n	%	n	%	n	%
9	Prevalence of comorbidities						N		%	
	0									

	1-3		
	≥ 4		
10	Presence of venous thromboembolism		
		Yes (%)	No (%)
	Pulmonary Embolism		
	Deep vein Thrombosis		

Table 6: Risk factors associated with developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital.

Variable	**Category**	**Screen for VTE**		**OR**	**P Value**
		Yes %	**No %**	**95% CI**	
Age	PE				
	DVT				
Weight	PE				
	DVT				
Height	PE				
	DVT				
BMI	PE				
	DVT				

Table 7: Tumor related risk factors associated with developing venous thromboembolism in patients with breast cancer in Kenyatta National Hospital.

Variable	Category	Screen for VTE		OR 95% CI	P Value
		Yes %	No %		
Stage of breast cancer	PE				
	DVT				
Pre- chemotherapy Hemoglobin level	PE				
	DVT				
Pre-chemotherapy leucocyte count	PE				
	DVT				
Number of chemotherapy cycles	PE				
	DVT				
Hospitalization	PE				
	DVT				
Surgery	PE				
	DVT				
Radiation	PE				
	DVT				

Table 8: Methods used in the management of venous thromboembolism amongst patients undergoing breast cancer treatment at Kenyatta National Hospital.

Sno	Characteristic	n %
16		
17		
18		
19		
20		

APPENDIX 3: WORK PLAN

Table 9: GANTT CHART

	JAN 2019	FEB 2019	MAR 2019	APR 2019	MAY 2019	JUNE 2019	JUL 2019	AUG 2019	SEP 2019	OCT 2019	NOV 2019
Identify and develop a research topic											
Research proposal writing											
Submit to the Ethics department											
Data collection											
Data analysis											
Write the first dissertation draft											
Submit dissertation											
Defense of dissertation											

Table 10: APPENDIX 4: BUDGET

S.no	Item	Unit cost (Ksh.)	No. Required	Total cost (Ksh.)
1.	Box file	200.00	3	600.00
2.	Pens	20.00	20	400.00
3.	Printing papers	800.00	3 reams	2400.00
4.	Air time	1000.00	1	1,000.00
7.	Printing	5.00	1500	7,500
8.	Binding	100.00	6	600.00
9.	Statistician	25,000	1	25,000
10.	Sub-Total			37,500.00
11.	Contingency (5% Total)			1,875.00
12.	Grand Total			**39,375.00**