MANAGEMENT AND OUTCOME OF VENOUS THROMBOEMBOLIC DISORDERS AMONG CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL

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U56/34437/2019

A research dissertation submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of the University of Nairobi.

DEPARTMENT OF PHARMACY

NOVEMBER, 2021

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SUPERVISORS' APPROVAL

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DEDICATION

This dissertation is dedicated to God for inspiring me and giving me knowledge. He has been my guide and strength throughout this program. I also dedicate this work to my mum, Tabitha Nyansiaboka Omwega for encouraging me and praying for me. To my brother and sisters whose numerous calls of encouragement made me work harder. To my husband, Evance Barracks for supporting me in all ways possible to ensure that I finish this program without any hitches. Lastly but not least, my little girl, Thandiwe Sulwe Barracks who inspires me to be a better version of myself. Thank you.

ACKNOWLEDGEMENTS

I would like to acknowledge with gratitude my supervisors Dr. David Gitonga Nyamu(PhD)and Dr. George Arthur Mugendi(PhD) for making the completion of this work possible. Their guidance and positive criticism carried me through from the proposal writing stage to the completion of this dissertation.

Special mention to Prof. Francis Abuga Ndemo, for being a great mentor and pushing me to try new exploits in the profession.

Special gratitude to my husband, my daughter and mother who have been a pillar of support throughout my studies. Their prayers have sustained me to this stage.

Finally, I would like to thank God for sustaining and guiding me through this whole process. Without His providence, I would not have made it this far.

OPERATIONAL DEFINITION OF TERMS

Anticoagulants

Refers to drugs used in the treatment of thromboembolism. They reduce or prevent coagulation of blood.

Deep Vein Thrombosis

DVT refers to a clot that arises in veins of the limbs especially the lower limbs. The leg becomes swollen and painful.

Pulmonary Embolism

Pulmonary embolism happens when a blood clot in the limbs loosens up and is carried via the circulatory system into the lungs.

Venous thromboembolism

This is a term that encompasses both DVT and PE. It refers to blood clots forming in the veins in the body.

ACRONYMS AND ABBREVIATIONS

APTT: Activated thromboplastin time

BMI: Body Mass Index

CRP: C-Reactive protein

DOAC: Direct Oral Anticoagulants

DVT: Deep Vein Thrombosis

INR: International Normalized Ratio

KNH: Kenyatta National Hospital

LMWH: Low molecular weight heparins

PE: Pulmonary embolism

PT: Prothrombin time

UFH: Unfractionated heparin

UoN: University of Nairobi

VKA: Vitamin K antagonists

VTE: Venous thromboembolic events

WHO: World Health Organization

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ABSTRACT

Background: Cancer is a well-known hypercoagulable state. Compared to patients without cancer, the incidence of venous thromboembolic events is 4 to 7 times higher among cancer patients. There is paucity of data on the assessment of the management and covariates of venous thromboembolic events (VTEs) among patients with cancer in resource constrained settings.

Objective: To characterize the management and outcome of venous thromboembolic disorders among Cancer Patients at Kenyatta National hospital.

Study Area and Setting: - Kenyatta National Hospital, oncology department

Participants: - Cancer patients with a diagnosis of VTE

Methodology: A retrospective cross-sectional design and random sampling were used to assess 250 files, which satisfied the inclusion criteria, from the health records department. Data on patient sociodemographic characteristics, types of cancer and treatment modalities, types and management patterns of VTE as well as outcomes of anticoagulation including level of anticoagulation, venous thromboembolic events recurrence and bleeding events were extracted from the files into a predesigned data collection tool.

Data Analysis: Raw data was entered into Microsoft excel 2016 to created database and exported to STATA version 13 for analysis. Descriptive analysis of variables such as marital status was done and presented as percentages while continuous variables such as age were analyzed and summarized using the mean, mode, median and standard variation. Inferential statistics using the Pearson's Chi-Square test or Fischer's test and logistic regression was used to determine the strength of association between the sociodemographic and clinical characteristics with the type of VTE, level of anticoagulation, VTE recurrence and occurrence of major bleeding episodes. Backward stepwise model building was used to achieve the most parsimonious model that explained independent predictors of the occurrence of bleeding events and statistical significance was assumed if the p-value was less than 0.05.

Results: Majority of the study participants were females (75.6%). The mean age of the participants was 54.4years (±15.4) years. Cervical cancer (30%) was the commonest malignancy and most patients (71.8%) developed VTE after 1 month of cancer diagnosis where the most prevalent thrombotic event was deep vein thrombosis, 234(93.6%). Warfarin was the principal agent prescribed for the management of the VTE (72.8%) but 5.6% patients had recurrence while 18.8% had major bleeding events. The duration of anticoagulation for most of the patients was

less than 3 months. Monitoring of patients was mainly through determination of INR and aPTT. Patients were poorly anticoagulated with only 33(16.6%) achieving optimal INR and only 7.6% had the aPTT values within the recommended range. The independent predictors of major bleeding events included comorbidities (AOR = 3.91; CI: 1.77- 8.63; p=0.001), gender (AOR=0.09; CI;0.02-0.04; p=0.02), history of surgery (AOR = 4.5; CI: 2.10-9.75; P <0.001) and history of radiotherapy (AOR = 6.13; CI: 2.19-17.23; P =0.001).

Conclusion: Most cancer patients suffer from DVT as opposed to PEs. Warfarin is the most used anticoagulant but there is poor anticoagulation control with majority of the patients being under-anticoagulated. However, the frequency of recurrence of VTE among cancer patients is low. The frequency of major bleeding events in cancer patients receiving anticoagulation therapy was high and majorly attributed to presence of comorbidities, gender, history of surgery and history of radiotherapy.

Recommendations: Anticoagulation practice among cancer patients should be improved. A specialized anticoagulation clinic that is focused solely on anticoagulation management may ensure that patients are followed up from a central place, adequate levels of anticoagulation are maintained and the negative outcomes of anticoagulation are noted earlier or prevented. A large prospective study to find out the outcomes of anticoagulation among cancer patients with VTE should be conducted so as to establish their accurate incidence rates and their associated risk factors.

CHAPTER ONE: INTRODUCTION

1.0: Background

The prevalence of venous thromboembolic events (VTE) is about 10 to 20% among cancer patients (1). Compared to patients without cancer, the incidence of VTE is 4 to 7 times higher among cancer patients(1). It is one of the leading causes of mortality in cancer patients (2).

Studies have indicated that certain factors increase the risk of VTE among cancer patients(3). For instance, cancer patients who are female, ≥65 years and African Americans have a higher risk of developing VTE(3). Others studies have indicated that tumor related factors such as cancer type and disease stage and biomarkers such as D-dimer and tissue factors have been linked to the development of VTE (4). Furthermore, research has shown that pancreatic, lung, stomach, kidney and brain cancers increase the risk of VTE development. Related studies have indicated that biomarkers such as platelet count, D-dimers, tissue factor and elevated c-reactive protein have also been implicated (3,4).

Treatment related factors that have also been linked to VTE development in cancer patients (4). Some of the treatment factors associated with development of VTE include major surgery, prolonged hospitalization, and the type of cancer therapy such as thalidomide, bevacizumab and lenalidomide (3). Furthermore, a study carried out in the United States of America (USA) found that patients on thalidomide had a two-fold increase in the development of VTE(4).

Management of VTE in cancer is varied. In the western countries, treatment guidelines recommend that the clinical course for anticoagulation therapy in cancer patients should be three months or six months or longer depending on the individual patient (5). Treatment beyond the 6 months is considered in patients who have metastatic disease and those on chemotherapy (5). The recommended treatment for VTE in cancer are low molecular weight heparins (LMWHs) for 3 to 6 months. Additionally, LMWHs are the drugs of choice for secondary prophylaxis of VTE in patients with malignancies (6). However, in a study carried out in the USA, over 70% of the cancer patients were treated with oral anticoagulants (warfarin and rivaroxaban) while only 25% of the patients were treated with LMWH (5).

Vitamin K antagonists (VKAs) with a target international normalized ratio (INR) of 2 to 3 can be used for long term anticoagulation in the cases where LMWH is not available (7).

VKAs such as warfarin are still prescribed widely in clinical practice but their use in oncology patients with VTE presents a great challenge. VKAs interact with other medications and also food which lead to changes in the INR which leads to a higher bleeding risk than LMWH(6).Studies have shown that direct oral anticoagulants (DOACs) such as rivaroxaban have similar safety and efficacy as warfarin in the treatment of cancer associated thrombosis. However, not much is currently known about their utilization in cancer patients (5).

Several Randomized Control Trials (RCTs) have been done to measure the outcomes of anticoagulation in cancer patients with VTE. When compared to non-cancer patients with VTE, cancer patients with VTE have a higher VTE recurrence rate. A number of trials have also documented that cancer patients on anticoagulation therapy have more frequent bleeding events (1). For instance, Comparison of LMWH Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with VTE (CLOT) and Comparison of LMWH and warfarin for the secondary prevention of VTE in patients with cancer (CANTHANOX) trials compared VKAs and LMWH in the management of VTEs in cancer (5,8). The CANTHANOX trial found mortality to be 22.7% in the group receiving warfarin and 11.3% in the group receiving enoxaparin. Out of the total 25 mortality cases in both groups, 6 (24%) died as a result of fatal bleeding in the warfarin group while there were no mortalities due to bleeding in the enoxaparin group (8).Major hemorrhage occurrence was 16% among the warfarin group and 7% among the enoxaparin group (8).

The CLOT trial which compared warfarin with dalteparin found that the dalteparin group had a VTE recurrence of 9% while the warfarin group had 17%. It also found mortality to be 39% among the patients receiving Dalteparin and 41% among the patients receiving warfarin (9). In 2015, the Comparison of Acute Treatments in Cancer Hemostasis (CATCH) trial showed that the incidence of VTE recurrence in patients receiving LMWH (tinzaparin) was 7.2% and 10.5% in patients receiving warfarin (10).However, the rates of major bleeding events were similar in both groups in the study(10).

Studies in Kenya and other resource limited settings on VTE among cancer patients remain scarce. The aim of the present research is to characterize the management and outcomes of VTE among cancer patients at Kenyatta National Hospital.

1.1 Problem Statement

The development of VTE in cancer is an indicator of poor treatment outcomes(11).Cancer patients who have VTE have an increased risk of early death, tumor progression, and decreased survival in the long term (11). Furthermore, venous thromboembolism is believed to be directly responsible for approximately 9% of cancer-associated deaths(4). Studies have indicated that VTE in cancer patients leads to interference in the chemotherapy regimens (4). VTE is associated with worsening quality of life and increased consumption of healthcare resources (4).

In the Western countries, studies have documented certain independent predictors of VTE development in cancer patients (4). The data available, though, is not conclusive because factors associated with VTEs in different types of cancers are scant. Moreover, in resource constrained settings, there is paucity of data on the correlates of VTEs in cancer patients.

International guidelines on VTE management among cancer patients recommend the use of LMWH over VKAs such as warfarin and LMWH over direct acting anticoagulants such as rivaroxaban(7). This is because evidence from clinical trials has shown that Warfarin is inferior to LMWH in reducing VTE recurrence in oncology patients (7). Furthermore, a study done by Khorana et al in 2016 indicated that warfarin accounted for approximately 50% all anticoagulants used among cancer patients in the US(12). In another study, 70% of the cancer patients with VTE were on oral anticoagulants while only 25% were on LMWH (5). However, anecdotal data suggests that warfarin still remains the most widely used drug in resource limited settings.

Data on the factors associated with the development of VTE in cancer patients and its management in Kenya is scant. There is no local data on the types of anticoagulants used in managing VTEs in different cancers, the duration of anticoagulation, and the outcomes of treatment. Due to scanty data on the above, the quality of anticoagulation therapy in the management and prophylaxis of VTEs in cancer cannot be guaranteed.

1.2 Research Questions

1. What are the prescribing patterns of anticoagulants among cancer patients with VTEs at KNH?
2. What is the level of anticoagulation management among cancer patients with VTEs at KNH?
3. What is the prevalence of recurrence of VTE among cancer patients at KNH?
4. What is the prevalence of major bleeding events among cancer patients on anticoagulation therapy at KNH?

1.3 Objectives

1.3.1 Main objective

To characterize the management and outcome of venous thromboembolic disorders among Cancer Patients at Kenyatta National hospital

1.3.2 Specific objectives

1. To describe the prescribing patterns of anticoagulants among cancer patients with VTE at KNH.
2. To establish the prevalence of recurrence of VTE among cancer patients at KNH.
3. To find out the level of anticoagulation management among cancer patients with VTE at KNH.
4. To find out the prevalence of major bleeding events among cancer patients on anticoagulation therapy at KNH.

1.4 Justification

Anticoagulation therapy among cancer patients with VTE is difficult as the patients have a higher risk of recurrence and bleeding when compared to other patient populations. The study aims at identifying factors associated with VTEs in cancer. Profiles of patients that are more likely to develop VTEs will be documented and used as a basis for prophylaxis to prevent and reduce recurrence. Modifiable factors can also be taken care of to prevent the development of VTE.

The proposed study will characterize the management of VTEs in cancers and their outcomes of therapy. The results of the study will help in identifying areas where there is little or no data as pertains to anticoagulation in cancer patients with VTE. This study is expected to

provide data on factors associated with VTEs, their management, and the outcomes of anticoagulant therapy in cancer patients. This information will lead to better monitoring of anticoagulant therapy in these patients and improved management of VTEs as the results of the study will provide a better understanding of the level of anticoagulation and the outcomes of anticoagulation therapy. This may form the database for future research.

The stakeholders that are likely to benefit from this study are oncologists and clinical pharmacists working in the oncology field. Oncologists will have access to more data on VTEs and their management in the setting of cancer. This will lead to improved management of these patients. Clinical pharmacists interested in anticoagulation in an oncology setting can offer monitoring services and management of anticoagulant therapy in this group of patients by coming up with a pharmacist led anticoagulation clinic where these patients will receive quality anticoagulation services.

1.5 Conceptual Framework

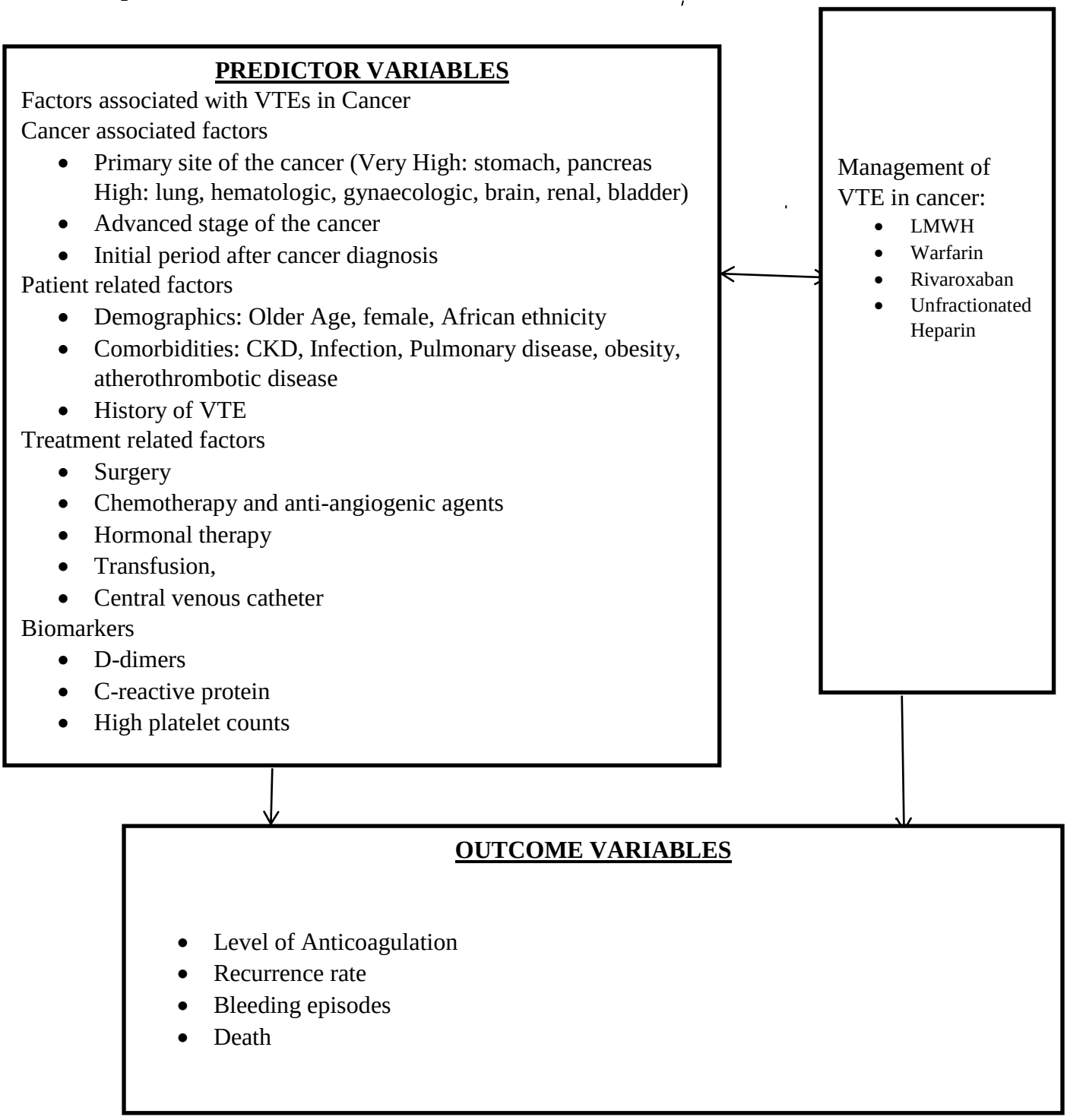

Fig 1. Conceptual Framework Showing the Interrelationship Between The Predictors And Outcome Variables Of The Study.

Key: CKD-Chronic Kidney Disease; VTE-Venous Thromboembolism

Factors associated with the development of VTE in cancer are those that predispose the patient to thrombosis. VTE in cancer will include DVT, PE or DVT, and PE combined in these patients. Advanced age of greater than 65 years, comorbid conditions and obesity are some of the patient-related factors that are linked to the development of VTE among cancer patients.

Certain chemotherapeutic agents such as cisplatin and bevacizumab have also been implicated in the development of VTE in this patient population. Thalidomide, erythropoiesis stimulating agents (ESA), platelet transfusions and hormonal therapy have been postulated to increase the risk of VTE development in cancer patients. Studies have shown that there is also some association between development of VTE and surgery and radiation therapy in cancer patients. Biomarkers associated with the development of VTEs include high platelet counts, elevated C-reactive protein levels (CRP) and D-Dimer levels. Cancer associated factors such as the site of the cancer, the staging and the duration since cancer diagnosis are also important factors.

The management of VTE in cancer will encompass all anticoagulants used in the treatment of VTE and therapy duration. The outcomes that will be measured in the study will be a recurrence, level of anticoagulation, major bleeding events and death.

1.6 Delimitations

The proposed study will only capture data on VTE among cancer patients only. As such the outcomes of this study may not be extrapolated to other patient populations with VTEs. Participants who were on anticoagulation therapy before they got diagnosed with cancer will not be included in the study even if they will have met all the qualifications since the study is only focused on patients who developed VTE in the setting of cancers.

The study will be carried out in Kenyatta National Hospital which is a large referral hospital but may not be a representation of all the hospitals managing cancer patients in Kenya. Data will be extracted from patient files using a questionnaire specifically designed for the proposed study. The questionnaire will only focus on the factors associated with VTEs in cancer, their management and outcomes. Therefore, any other data that does not fall into these categories will not be extracted from the patient files. The proposed study results will be generalizable to cancer patients who have VTE and are on anticoagulation therapy. Patients who do not meet these conditions will not benefit from the results of the study.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

The purpose of this Chapter is to interrogate available literature on the determinants and management of VTE in cancer patients. It will also cover the various outcomes of anticoagulation therapy in these patients. This section will first define VTE and its development in cancer patients and then, outline the global, regional and local view of the determinants of VTE, management and outcomes.

2.2 Definitions of VTE

VTE is a term that encompasses both pulmonary embolism(PE) and deep vein thrombosis(DVT) (6). It is a condition whereby the blood has a tendency to clot in the venous circulation. The reasons for this observation are described in the Virchow's triad. All components of Virchow's triad (blood stasis, hypercoagulability and endothelial injury) are present in cancer patients (13). Furthermore, abnormalities in the anticoagulation pathway and platelet activation all contribute to the hypercoagulability status of these patients(13).

2.3 Epidemiology of VTE in cancer patients

According to WHO, the burden of cancer is on the rise globally especially in low and middle income countries(14). Studies have shown that the risk of VTE is 4 to 7 times higher in cancer patients than the general population(11).In the US, the incidence of VTE among cancer patients studied for over 10 years (1993 to 2012) was found to be 3.8% (15). Another retrospective cohort study in the US reported VTE incidences of up to 7.8% among cancer patients(16).These results were different from those obtained by a study in the United Kingdom (UK) which also followed cancer patients for 10 years and found the incidence to be 5.8 per 100 person years(17).

Due to low incidence of genetic polymorphisms, prevalence of VTE is lower in people of Asian descent than in African Americans and Caucasians. This has led to very few studies being done on cancer associated VTE among Asians(18). However, in Taiwan, a retrospective cohort study recorded an incidence of 3.2% of VTE cases among cancer patient (19). This was similar to the rates recorded in the US and the UK. Of note is that in this study, cancer of the liver, pancreas, lung, multiple myeloma and non-Hodgkin's lymphoma made up 67.6% of all the VTE cases(19). In Korea, a study looking at VTE in advanced gastric cancer reported an incidence of 3.5% (20).

Studies on VTE in cancer among Africans provide varying prevalence. For instance, in Egypt, a retrospective study on VTE in cancer found that out of the 2500 cancer patients included in the study, 570 patients (22.8%) had VTE(21).While in Nigeria,12.2% of the patients with DVT had a malignancy(21). Related study done in Uganda found that 5% of the post-surgery patients with DVT had cancer. In Senegal, a study showed that 3.81% of patients with cancer will develop VTE. Another study done in South Africa reported that 4.1% of the DVT patients included in the study had cancer(21). A study done in Uganda reported a 6% prevalence of lower limb DVT in breast cancer patients(22) while in Ethiopia 26.4% of the patients developed recurrent DVT while being hospitalized (23).

In Kenya, there is paucity of data on cancer associated thrombosis. A study done in KNH on admitted cancer patients found a DVT prevalence of 10.9%(24). Another study done among breast cancer patients found the prevalence of VTE to be 2.65%(25). These results differ to those obtained from breast cancer study in Uganda which reported a 6% prevalence of lower limb DVT(22).

2.4 Determinants of VTE development among cancer patients

In the United states, a review assessing the risk factors for VTE identified that patients with malignancies of the uterus, pancreas, kidney, stomach, lung and brain posed a greater risk of VTE than the other cancers(26). A case control study found out that hematologic cancers were associated with the greatest risk of developing VTE then lung and gastrointestinal cancers in that order(26). Local data differs with these findings as the study done by Habib *et al.* in hospitalized patients at KNH found the prevalence of DVT to be highest among those with gynecological cancers (44.7%) with the highest prevalence being in cervical cancer (24.1%) followed by uterine cancers (10.3%) and ovarian cancer(10.3%)(24). In male patients, patients with prostate cancer had the highest cases of DVT (10.3%). Gastric cancer and breast cancer both accounted for 10.3% of the cases each (24).

Although the risk of VTE is markedly elevated in cancer patients, there exists variations between patients and also within the same patient at different periods as the disease progresses(26). For instance, advanced cancer stage has been linked to an increased risk in VTE development in surgical patients. However, studies have shown that in ambulatory cancer patients who have good performance status and are on chemotherapy, stage is not a determinant of VTE(26). Also a study on ovarian cancer among outpatient patients did not find a link

between stage and VTE(26). A study carried out in Ethiopia only identified malignancy as a risk factor for VTE but did not look at VTE in the different types of malignancies and their staging (27). This is also observed in several studies from Nigeria, Cameroon and Uganda(28). Locally, a higher prevalence of VTE was identified among the group of patients with advanced cancer; stage 3 (44.8%), followed by those with stage 4 (41.4%) in hospitalized patients (24).

The risk of developing VTE peaks in the first ninety days after the diagnosis of cancer(26). This may be attributed to the many interventions initiated during this period but even among those patients receiving chemotherapy only, the risk has been found to be higher during this initial period(26). Locally, a study on VTE in breast cancer at KNH found that risk of VTE among these patients was highest 6 months or more after diagnosis(25). The study done in KNH among hospitalized cancer patients also noted that VTE tends to occur within a year after diagnosis(24).

Chemotherapy has been associated with up to 6 times higher risk of VTE(26). When thalidomide was given together with chemotherapy and dexamethasone, it was found increase risk (12 to 28%) of developing VTE(26). Platinum based regimens such as Cisplatin, doxorubicin, lenalidomide and bevacizumab have been significantly associated with an increased risk (26). Supportive therapy like erythropoiesis stimulating agents (dapoeitin/epoetin), blood transfusions and platelet transfusions has also been shown to increase the risk(26). This is contrasted in the study carried out on breast cancer at KNH which found no significant association between chemotherapy and VTE(26). Of the cancer patients with VTE hospitalized in KNH, 45.1% were on chemotherapy(24). The study, however, did not look at the individual drugs and how they were associated with VTE.

Few studies have evaluated the association of radiation therapy and risk for VTE in the USA and there seemed to be no association (26). This is in contrast to local studies which find an association between the two. In KNH, 41.3% of the cancer patients with VTE were on radiotherapy(24). Another study on VTE in breast cancer found a significant correlation between radiotherapy and the risk of developing VTE(25).

Surgery is an established risk factor for VTE. A recent study of cancer patients who have undergone surgery in the US recorded the incidence of VTE at 40% in 21 days(26). This was also seen locally where in breast cancer, surgery was associated with development of VTE(25). In hospitalized cancer patients at KNH, an association between the two was made(24).

Some biomarkers have been linked to the development of VTE. In a prospective observational study in the US, platelet counts of ≥ 350,000/microliter and Leukocyte counts of ≥ 11,000 per microliter were found to increase the risk of VTE development(26). Elevated D-dimer levels and C-reactive protein (CRP) of >400 mg/dl have also been associated with VTE in cancer(26). None of the local studies sought to find out how these biomarkers relate with the development of VTE in cancer patients within our setup.

A study among hospitalized cancer patients in the US found that an advanced age of ≥ 65 years of age was associated with a higher risk of VTE(12). This is replicated in local studies where among hospitalized cancer patients in KNH, an age of ≥45 years was one of the factors associated with VTE(24). However studies in the USA among ambulatory patients showed no significant association between age and VTE development(26). Female cancer patients were found to have an increased risk of VTE in comparison to males(26). The findings were similar to local studies where the female patients also had a higher risk(54.5%) when compared to males (45.5%)(24).

Comorbidities with a strong association to VTE include; anemia, obesity, renal disease, infection, arterial thromboembolism and pulmonary disease(26). In a study of ovarian cancer patients, the risk of VTE increased from 2.1 in patients with a single comorbidity to 3.9 in patients with three comorbidities (26). This observation was similar to a local study on breast cancer which found out that the number had a significant association to the development of cancer(25). In the study of hospitalized cancer patients at KNH, 55.2% of the patients with DVT had a comorbid condition (24).

2.5 Management of VTE in cancer

Current guidelines for the treatment and prophylaxis of cancer associated thrombosis recommend the use of LMWH for 3-6 months. They also recommend the practice of extended anticoagulation therapy (more than 6 months) in metastatic disease(5). Some guidelines recommend indefinite continuation of anticoagulant therapy provided there is evidence of active cancer(2). In the event of a recurrence, it is recommended that the dose of the LMWH be increased by 20-25% in patients taking LMWH or switch from VKA to LMWH in the patients who are taking VKA(29).

For thromboprophylaxis, treatment guidelines recommend that parenteral anticoagulation therapy be used. Treatment should start 2-12 hours before surgery and then continued for at least

a week after surgery(2). A systematic review showed that after an abdominopelvic surgery, extended thromboprophylaxis of 2 to 6 weeks reduces the risk of VTE by approximately 50% and it is now recommended that this class of patients receive anticoagulant therapy for 4 weeks(30). In ambulatory patients who are seen as outpatients, guidelines discourage routine prophylaxis of VTE(30).

Treatment of VTE is done in two stages; acute treatment (3-6 months) and extended treatment (>6 months)(30). For quite some time now LMWH has been the drug of choice for acute cancer associated thrombosis. In the CLOT study where LMWH was compared to VKAs, LMWH showed a significant reduction in the recurrence rate of VTE among cancer patients(30). Other studies such as the CATCH study showed a decrease in non-major bleeding with LMWH(30).

A VTE cancer trial which compared anticoagulation outcomes with edoxaban or dalteparin showed that initiation treatment with dalteparin and for five days followed by edoxaban was not superior to dalteparin for 1 month. This was with respect to recurrence rate of VTE and major bleeding events(31). In another trial that compared dalteparin to rivaroxaban, the latter was found to have reduced recurrent VTE rates(32).

VTE clinical guidelines published before 2018 included few recommendations on the use of DOACs for cancer associated thrombosis(33). However, studies have shown that DOACs are non -inferior to VKAs and had similar efficacy to LMWH in the treatment of VTE in cancer(33). Emerging real world data shows that even before guidelines supported their use in the treatment of VTE in cancer, DOACs were being used(33). In a large retrospective study of cancer patients, VTE recurrence was lower by 28% in participants taking rivaroxaban than those taking LMWH. It was also lower by 26% in patients who were in the rivaroxaban group when compared to the patients on warfarin(33). So far the only DOACs that have been used in RCTs in cancer populations are edoxaban and rivaroxaban. Due to the difference in mechanism of action and clearance, a class effect should not be assumed and Dabigatran and Apixaban should not be routinely used in these patients(34).

A retrospective study evaluating prescription patterns for the treatment of cancer associated thrombosis reported that 50% of patients were prescribed warfarin, 40% LMWH and 10% other anticoagulants such as DOACs(12). The findings are similar to those of another retrospective cohort study in the USA where warfarin was prescribed in 47.7% of cancer patients

with VTE followed by LMWH (25%) and rivaroxaban (24.1%) (5). In Kenya, a study on breast cancer found that 80% of the patients were on warfarin while another 80% were managed using a combination of warfarin and LMWH(25). There was no documentation of the use of rivaroxaban in the treatment of VTE in breast cancer in the Kenyan study.

In the study carried out in the USA, the choice of anticoagulant varied with the site/type of cancer (12).In those patients being treated with warfarin, 33% were pancreatic cancer patients and 65% were prostate cancer patients. In those being treated with LMWH 24% ,were prostate cancer patients and 54% were suffering from pancreatic cancer (12). There were differences in prescribing patterns according to cancer stage, LMWH prescription rates were higher in stage IV than in stage III cancer(12). In a retrospective study in the USA, it was noted that more patients with comorbidities were treated with LMWH when compared to rivaroxaban and warfarin(5). The Kenya studies did not look at the prescribing patterns on anticoagulants with relation to the type and stages of cancer.

2.6 Level of Anticoagulation

Prothrombin time(PT) is a routine test that can be used to monitor Rivaroxaban. INR using rivaroxaban sensitive thromboplastin can also be used(35). Drug specific anti factor Xa has also been used to measure the plasma levels of the drug. Activated partial thromboplastin time(APTT) can also be used but is less sensitive than PT(35). LMWH can be monitored using anti factor Xa but is not recommended unless the patient has an increased bleeding risk, in renal failure, pregnancy and has extremes in body weight (36). The level of anticoagulation for unfractionated heparin (UFH) on the other hand can be monitored using APTT or anti factor Xa(36).

A study done by Nyamu *et al* in KNH reported that only 27.5% of the patients included in the study were adequately controlled (37). The study largely focused on warfarin therapy and relied on INR readings to assess the level of anticoagulation. There are no studies locally showing the level of anticoagulation in VTE patients anticoagulated with the other

2.7 Outcomes of Anticoagulation therapy in cancer patients

There are three outcomes that can arise from the management of VTE in cancer using anticoagulants; recurrent VTE, bleeding and death. Cancer patients have difficulty controlling the international normalized ratio (INR) which may be attributed to several factors including cancer associated hypercoagulability and drug- drug interactions(38). A prospective cohort study

done in the USA to evaluate the effectiveness of warfarin among cancer patients found that these patients spent less time in the target INR range and hence experienced more thrombotic events(38).

In a systematic meta-analysis conducted to evaluate the safety (bleeding events) and efficacy (recurrent VTE) of anticoagulation therapy among cancer patients, LMWH and DOACs were associated with a lower rate of recurrence when compared warfarin (39). These results reflected those of another study which concluded that the safety and efficacy of DOACs and LMWH are comparable (40).There was no difference in bleeding events and mortality between warfarin and LMWH(39).DOACs on the other hand had higher risk of major bleeding (39). No local data about the outcomes of anticoagulation therapy in cancer patients could be found.

In a study done in the US, the recurrence rate of VTE among cancer patients was found to be 20.1 %(41). The study also found out that the recurrence rate was lower among patients who had been treated for a longer duration of treatment (more than 3 months)(41). In another study comparing recurrence of VTE in patients being treated with different anticoagulants, 13% of the patients treated with rivaroxaban developed recurrent VTE while those treated with warfarin and LMWH had the same recurrence at 18%(42). In the CLOT trial, VTE recurrence was 17% among the warfarin group and 9% among the dalteparin group (9). This was higher than the findings obtained by the CATCH trial which showed the incidence of VTE recurrence to be 10.5% in the warfarin group and 7.2% in the LMWH group (10).

In the US-based study by Khorana, the rate of bleeding events among cancer patients was 12.2%(41). Majority of the bleeding events occurred in patients who had received treatment for less than 3 months(41). Another study found that the rate of bleeding events was higher in patients who had been anticoagulated for 6 months (8.7%) than those who had been anticoagulated for 3 months (5.9%)(42). These bleeding rates are similar to what was found during the CLOT study (8.5%) and higher almost thrice what the CATCH study reported(3%) (42). In the CANTHANOX study the occurrence of major hemorrhage was 16% among the warfarin group and 7% among the enoxaparin group (8). In a study conducted in the US, warfarin had a higher bleeding incidence at 20.2%, followed by Rivaroxaban at 16.7% then apixaban at 14.5% and finally LMWH at 13.2%(43). The results of this study were comparable to the Hokusai study(31). They are also consistent with another study that found that DOACs have a higher bleeding risk (39).

2.8 Gaps in Literature

Several gaps exist in the studies included in the literature review. No data that relates specific chemotherapy agents with VTE development is available locally. Lastly but not least, there is little data on the outcomes of anticoagulation therapy among cancer patients in Kenya. This study will seek to provide data on all the gaps identified in this literature review.

CHAPTER THREE: METHODOLOGY

3.1 Perspective of Research Methodology

This chapter outlines the methods of research that were followed in this study. It describes the research design that was used and explains why it is a suitable choice. It states the location of the study, the target population and the study population. This section will also provide information on the inclusion and exclusion criteria of the participants and the sampling technique used. The instruments that were used in the study will be described and discussed. Data collection techniques and how data was analyzed will also be discussed in this section. Lastly, the ethical considerations that were followed in the study will be discussed.

3.2 Research Design

The study design was a retrospective cross-sectional study. The primary use of cross-sectional studies is to determine prevalence. They are also used in inferring causation (44). This is what informed the choice of a cross-sectional study being used as the research design in this case. The study was quantitative in nature with the prevalence of the determinants and anticoagulants used were quantified.

Cross-sectional studies are quick and cheap to carry out since there is no follow up(44). Due to time constraints, a research design that is quick and affordable to carry out is the best option.

3.3 Study area and site

The study was carried out at Kenyatta National Hospital which is situated in Nairobi. It has a large bed capacity of 1800 beds. According to the 2019 census, Kenya has a population of 47.5 million people with Nairobi being the most populous county at 4.39 million(45). It is the largest referral hospital in the country which serves 47.5 million people from all over the country. The study participants were from KNH and therefore they were from all parts of the country with diverse characteristics and backgrounds.

The hospital is also a teaching hospital for university of Nairobi (college of health sciences), Kenya medical training college and other related tertiary institutions. The collaboration between the University of Nairobi school of pharmacy and KNH makes it easily accessible to clinical pharmacy students throughout the study period. The study site was the oncology department which serves a large number of patients annually. Since it is a referral

hospital, all types of cancers were well represented. KNH also keeps records for years and hence easy accessibility to patient files needed for the study.

3.4 Target Population and Study Population

The target population in this study was all cancer patients with VTE in Kenya. The study population was cancer patients with VTE at KNH from January 2016 to December 2020.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

The inclusion criteria for participating in the study included the following:

- Any cancer patient with VTE that has been diagnosed through imaging or clinical findings.
- Cancer patients receiving anticoagulant therapy for the management of VTE

3.5.2 Exclusion criteria

The exclusion criteria will include the following:

- Cancer patients who do not have a confirmed VTE diagnosis but are on prophylactic anticoagulants to prevent development of VTE.

3.6 Sample Size Estimation

3.6.1: Calculation

The main outcome variable is the recurrence of VTE among cancer patients. Assumptions will be derived from a study by Khorana in the US who found the recurrence of VTE in cancer to be 20.1%(41).The Cochran formula (46) will be used;

$n= (z^2\times p(1-p))/d^2$ where;

n= sample size

z= statistic corresponding level of confidence (1.96)

p=expected recurrence of VTE in cancer,20.1% (47).

d= estimated error (0.05)

Substituting this in the formula gives a sample size of 246 as shown below:

$n= (1.96^2 \times 0.2(1-0.2))/0.05^2 =$**246**

3.6.2: Availability of data (Ref: KNH Records)

From the available data at the records department, the number of cancer cases from January 2016 to December 2020 is 15,767. Among these patients 345 had DVT and 51 had PE.

The total number of VTE cases among cancer patients during this time frame is therefore 396. The estimated prevalence of VTE in cancer according to these estimates is 2.5%. The data available at the records department only includes patients who have ever been admitted. It does not include outpatients who if added to 396 will increase the number of cancer patients with VTE. Therefore, the sample size of 246 was be met.

3.7 Sampling Method

Simple random sampling was used to get the required sample for the research. All files of patients diagnosed with VTE in cancer between January 2016 and December 2020 were listed. They were checked to see if they satisfy the inclusion criteria. Those that satisfied the inclusion criteria were tagged using unique identification numbers. Random numbers generated by a statistical software were assigned to each file so as to get the study sample. Files missing adequate data were excluded from the data and replaced by files from the un-sampled files.

3.8 Participants Recruitment and Consenting Process

All the records were obtained from the KNH records department. Since the study was retrospective review of records, no consenting of participants was required.

3.9 Research Instruments and Data collection

An eligibility form was used to determine the files to be included in the study. A structured questionnaire was used to extract information from the files. The questionnaire was divided into 5 parts. Section A was biodata and section B contained social and demographic characteristics. Section C contained the determinants of VTE among cancer patients (patient related, treatment related, biomarkers and cancer associated). Section D contained information about the anticoagulants used in the treatment of VTE among cancer patients (type of anticoagulant and duration of anticoagulation). Section D focused on the outcomes of anticoagulation therapy (level of anticoagulation, bleeding events, recurrence of VTE and death that can be attributed to VTE). Data collection was done by the principal investigator. Medical records and medication chart reviews were used as sources of data for this study. Data about patient characteristics and medications that they were on was gotten from the files.

3.10 Piloting of the study

A pilot study was done so as to test the data extraction tool for reliability. The study used the rules of thumb method by Julious which suggests a minimum sample size of 12 in pilot studies(48). Only the files of patients who met the inclusion criteria was used. It tested how long

it took to extract data from the files, whether the questions were clear or ambiguous and whether the correct wording was used in formulating the questionnaires. Any identified problems were remedied.

3.11 Quality Assurance, Validity and Reliability of the Collected Data

For quality to be assured through all stages in the study, extracted data from the files were counterchecked by another independent research assistant. Data was stored in a password protected computer and flash drive that was only accessible to the supervisors, the investigator and statistician.

The research instrument was tested for content validity by giving the questionnaire to the supervisors and pharmacist working at the Oncology department of KNH. They checked on how accurately the questions in the questionnaire elicited the information being sought by the study. To ensure reliability, each question was accurately and carefully phrased to avoid ambiguity. The pilot study also ensured reliability of the questionnaire.

3.12 Internal and External Validity

Internal validity is defined as the extent to which the results obtained in a study represent the truth in the population being studied(49) . To increase internal validity, adequate recruitment strategies were ensured by careful selection of participants for the study. Adequate data was collected and carefully analyzed. Lastly, adequate sample size that was a representative of the target population was calculated.

External validity deals with the generalizability of the study results. It is used to deduce whether the study results can be applied to similar patients who are in a different setting(49). To ensure external validity, a broad inclusion criterion was used so that the population in the study would have a close semblance of real life patients in other set ups.

3.13 Study Variables

The independent variables in this study were the determinants of VTE in cancer patients and the anticoagulants used in the management of VTE. Determinants for VTE in cancer were defined as those characteristics that are associated with the development of VTE in cancer. The first determinants were patient related. The data variables were age, sex, comorbid conditions and body mass index (BMI). The second determinants were cancer associated; the stage of cancer, the site of the cancer and time since diagnosis of cancer.

The third group of determinants were treatment associated; medicines used, radiation and surgery were the data variables. The fourth group of determinants were the biomarkers; d-dimers, CRP and platelet counts. Anticoagulants were defined as the medications used in the treatment of VTEs. The data variables were type of anticoagulant (warfarin, rivaroxaban, enoxaparin), the duration of anticoagulation and INR values of patients on warfarin.

The dependent variables were the outcomes of anticoagulation therapy. They will be major bleeding, recurrent VTE cases and mortality. Major bleeding events were defined as any bleeding event such as from the gastrointestinal, genitourinary, cerebral or any other site that will necessitate hospitalization when a patient is on anticoagulation therapy. VTE recurrence was defined as the development of PE or DVT among cancer patients during or after treatment with anticoagulants.

3.14 Data management

3.14.1 Data processing

A total of 20 files were targeted in a day. Using the designed questionnaire, relevant data was extracted from the files chosen. The data was fed into a password protected excel sheet daily until the process of data collection was done. The principal investigator then cleaned and verified the data before analyzing.

3.14.2 Statistical methods

Organization, coding and analysis of data will be done using STATA 13.

3.14. 2. 1 Univariate, Bivariate, and Multivariate analysis

Univariate analysis was done by use of descriptive statistics. This was used to present and describe data on determinants, anticoagulants used and the frequency of the outcomes of anticoagulation therapy. To summarize the data, measures of central tendency (mode, mean, median and standard deviation) will be used to describe the frequency of the data.

Inferential statistics was used to measure the strength of the association between the determinants, the type of anticoagulants and the outcomes of anticoagulation therapy. The results of the bivariate analysis were subjected to multivariate analysis so as to determine the independent predictors of developing the outcomes of interest. The results were then summarized using tables.

3.15 Ethical Considerations

The proposal was presented to the KNH-UoN Ethics and Research Committee for approval. Once approved, permission was sought from the KNH oncology department and the KNH records department. Since data was extracted from patient files, informed consent was not being sought from the patients.

To maintain the privacy and confidentiality of the study participants, their data was de-identified by not including the names of the patients on the questionnaire. The data was stored in a password protected laptop with only the principal investigator having the password. For back up purposes, data was also being stored in a flash drive that was kept in a safe and secure place.

3. 16 Dissemination Plan

The research findings will be shared to the University of Nairobi College of Health Sciences and the school of pharmacy so that it can be available to other students who would want to do research in the same area. A copy of the research will be given to Kenyatta National Hospital, Oncology department so that they can utilize the study findings to improve the management of cancer patients with VTE. The research will be presented in various conferences. The study will also be published in a journal so as to ensure that the study findings are available to various researchers globally.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter discusses the sociodemographic characteristics of the participants, the various types of cancers and comorbidities. It also describes the prevalence of VTEs, the pharmacological trends of managing VTEs, the prevalence of bleeding events among patients and the level of anticoagulation. There is also a summary of various covariates of the level of anticoagulation, the recurrence of VTEs, the bleeding episodes, and mortality among cancer patients.

4.2 Sociodemographic Characteristics of the Participants

Most of the participants were females (n=189, 75.6%), single (n=156, 62.4%) and Christians (n = 239, 95.6%). Most of them had a primary level of education (n = 155, 62.0%), have never used alcohol (n=223, 93.2%) or tobacco (n=223, 93.2%). Majority were aged 37-55 years (n=113, 45.0%) and unemployed (n=106, 42.4%) (Table 1).

Table 1: Sociodemographic Characteristics of the Participants (N = 250)

Variable	Frequency, *n* (%)	Variable	Frequency (%)
Sex		**Education Level**	
Male	61 (24.4%)	Primary	**155 (62.0%)**
Female	**189 (75.6%)**	Secondary	77 (30.8%)
		Tertiary	18 (7.2%)
Age (Years)		**Employment**	
6 – 36	22 (8.8%)	**Status**	106 (42.4%)
37 – 55	113 (45.0%)	Unemployed	44 (17.6%)
56 – 74	89 (35.5%)	Employed	100 (40.0%)
>74	26 (10.4%)	Not Specified	
Mean ± SD	54.4 ± 15.4		
Marital Status		**Alcohol Use**	
Married	79 (31.6%)	No	**223 (89.2%)**
Single	**156 (62.4%)**	Yes	27 (10.8%)
Divorced	3 (1.2%)		
Widowed	9 (3.6%)		
Separated	3 (1.2%)		
Religion		**Tobacco Use**	
Christian	**239 (95.6%)**	No	**233 (93.2%)**
Muslim	5 (2.0%)	Yes	17 (6.8%)
Other	6 (2.4%)		

4.3 Clinical Characteristics of Participants

Most participants had undergone radiotherapy (n=148, 59.2%), received chemotherapy (n=233, 93.2%), and central venous catheter insertion (n=227, 90.8%). Most participants had no comorbidities (n=134, 53.6%), no past history of VTE (n=218, 87.2%), surgery (n=162, 64.8%) or blood transfusion (n=143, 57.2%) (Table 2).

Table 2: Clinical Characteristics of the Participants

Variable	Frequency
History of Radiotherapy	
No	102 (40.8%)
Yes	**148 (59.2%)**
History of Surgery	
No	**162 (64.8%)**
Yes	88 (35.2%)
History of Chemotherapy	
No	17 (6.8%)
Yes	**233 (93.2%)**
Blood Transfusion	
No	**143 (57.2%)**
Yes	107 (42.8%)
Central Venous Catheter	
No	23 (9.2%)
Yes	**227 (90.8%)**
History of VTE	
No	**218 (87.2%)**
Yes	32 (12.8%)
Presence of comorbidities	
No	**134 (53.6%)**
Yes	116 (46.4%)

4.3.1 Types of Cancers among study participants

The most prevalent cancers were cervical (n=75, 30.0%) and breast (n=18, 7.2%) followed by ovarian (n=18, 7.2%), prostate (n=15, 6.0%) and colon (n=10, 4.0%) in that order (Figure 2).

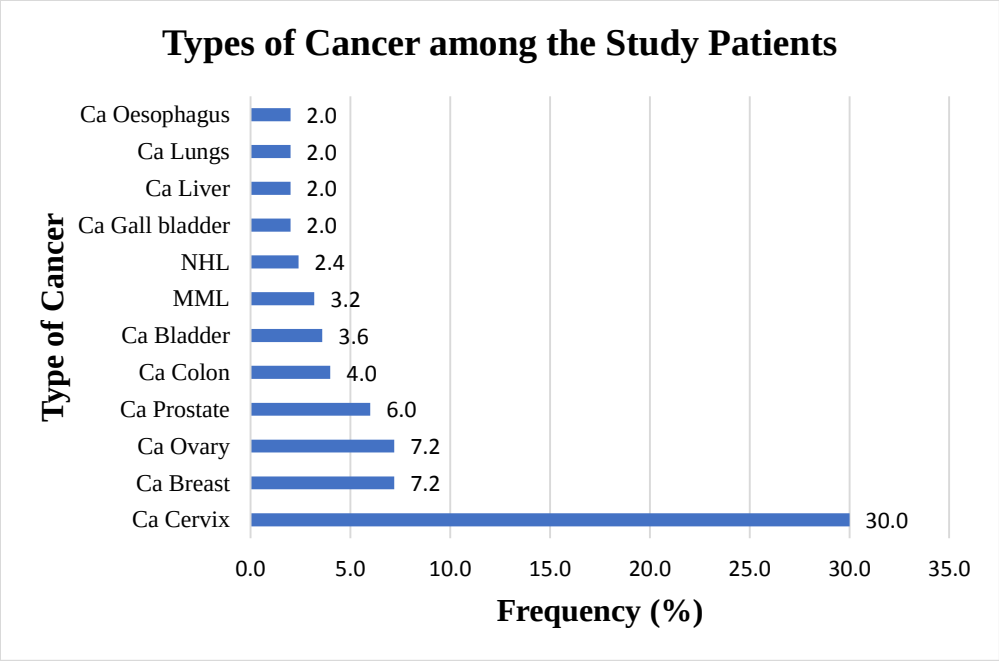

Fig 2: Types of Cancers among the Participants (N=250)

KEY: Ca – Cancer, MML – Multiple Myeloma; NHL – Non-Hodgkin's Lymphoma.

4.3.2 Comorbidities among participants

One hundred and sixteen (46.4%) of patients had comorbidities. Out of the 116 patients, majority, 85 (73.3%) had one comorbidity. The most common comorbidities included anaemia (26.0%), hypertension (14.9%), retroviral disease (9.7% and diabetes mellitus (8.4%) (Figure 3).

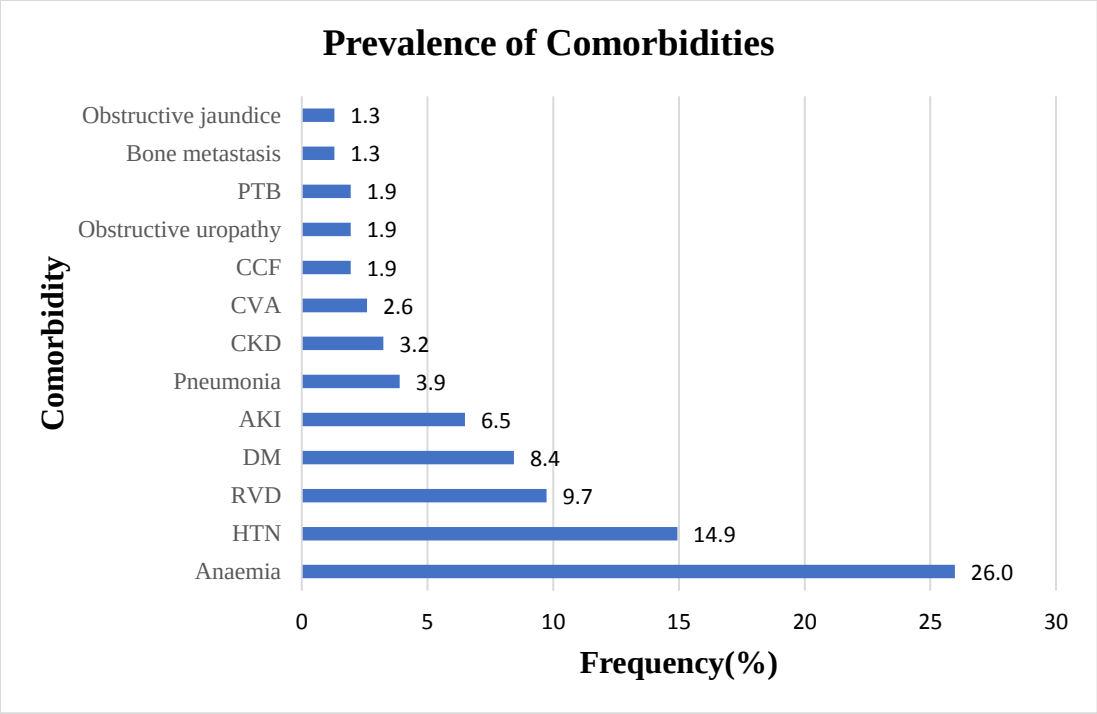

Fig 3: Prevalence of comorbidities among study participants

KEY: AKI – Acute kidney injury, CCF – Congestive cardiac failure, CKD – Chronic kidney disease, CVA – Cerebrovascular accident, DM – Diabetes Mellitus, HTN – Hypertension, PTB – Pulmonary tuberculosis, RVD – Retroviral disease.

4..3.3 Anticancer Drugs Used among the Study Patients

Eighty-one patients were using anticancer agents. The most commonly prescribed drugs included flutamide (n=20, 24.7%), lenalidomide (n=19, 23.5%) and cyclophosphamide (n=11, 13.6%) (Figure 4).

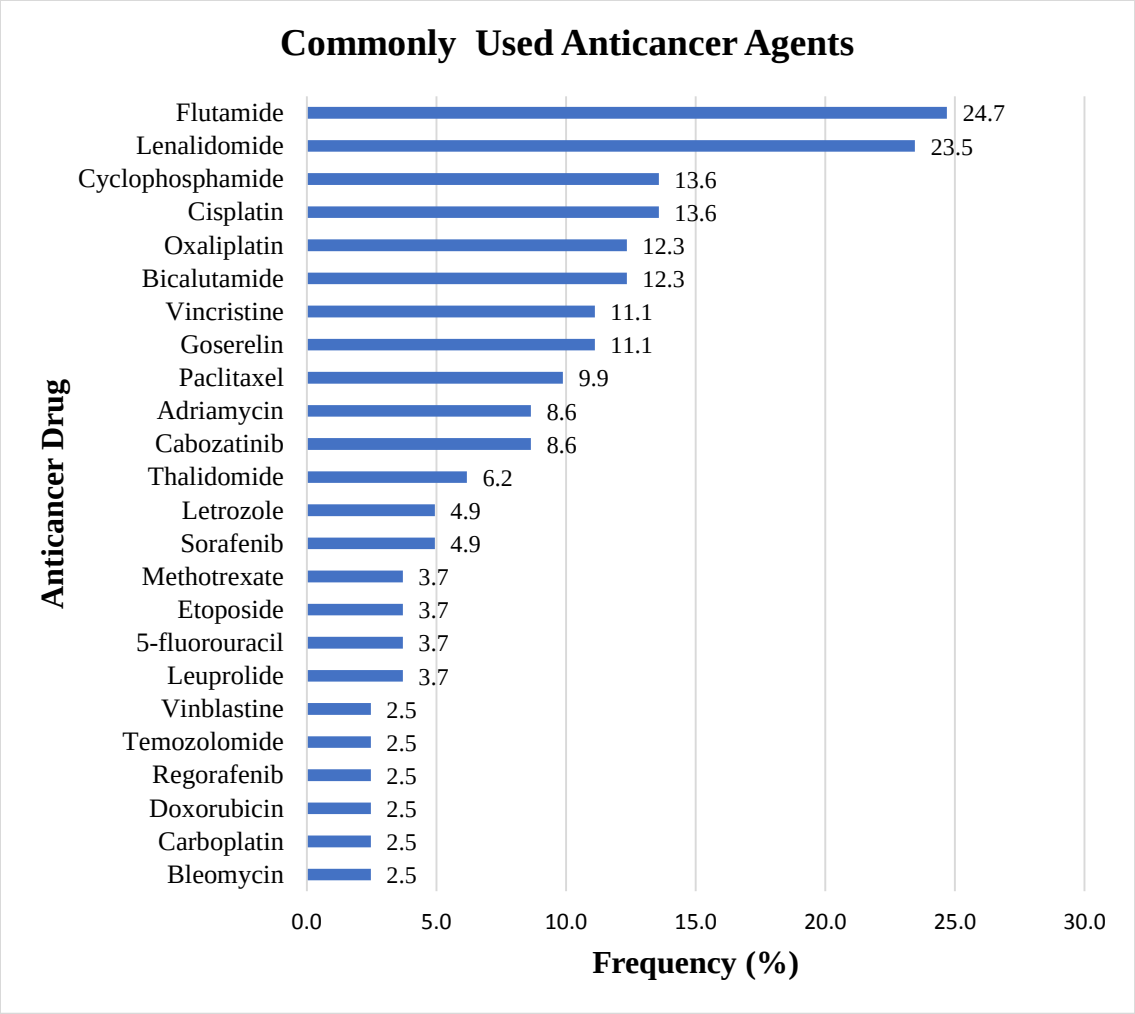

Fig 4: Commonly used Anticancer Agents among study participants

4.3.4 Other Commonly Used Drugs among study participants

Some of the other commonly used drugs besides the antineoplastic agents included metoclopramide (n= 70, 28.0%), ondansetron (n=45, 18.0%), tramadol (n=44, 17.6), paracetamol (n=38, 15.2%), dexamethasone (n=37, 14.8%), lactulose (n=36, 14.4%), ceftriaxone (n=29, 11.6%), and dihydrocodeine (n=27, 10.8%) in that order (Figure 5).

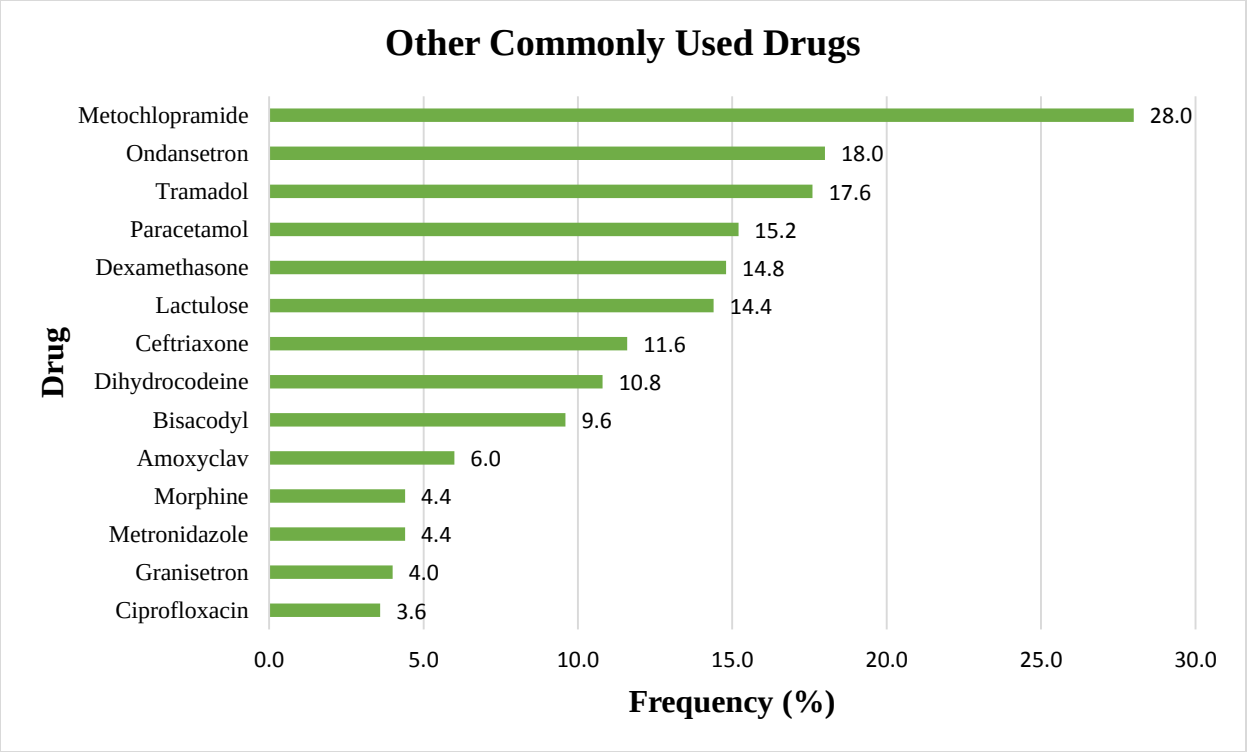

Fig 5: Other commonly used drugs

4.3.5 Onset of Venous Thromboembolism after Cancer Diagnosis

Two hundred and thirty-four patients (93.6%) had DVT, while 16 (6.4%) had PE.

After diagnosis, most participants experienced VTE after one month (n=173, 71.8%), two months (n=21, 8.71%), and three months (n=13, 5.4%). By the end of 12 months after cancer diagnosis, 232 (92.8%) of the participants has already experienced either DVT or PE (figure 6).

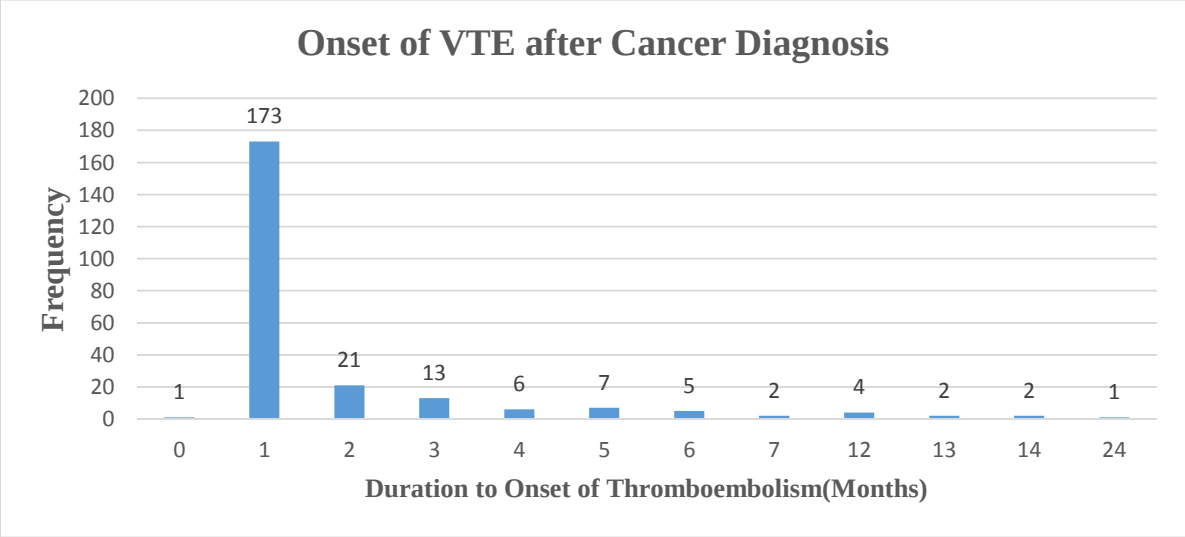

Figure 6: Onset of VTE after Cancer Diagnosis

Participants who had no central venous catheter (CVC) had a delayed onset [median 2, IQR (1,13) months] of development of VTE after being diagnosed with cancer compared to those with a CVC (Table 3).

Table 3: Median Duration (months) of Development of VTE after Diagnosis of Cancer

Variable	Median Duration (months)	Variable	Median Duration (months)
Sex		**Alcohol Use**	
Male	1, IQR (1, 2)	No	1, IQR (1, 2)
Female	1, IQR (1, 2)	Yes	1, IQR (1, 3)
Age (Years)		**Tobacco Use**	
Less than 55 years	1, IQR (1, 2)	No	1, IQR (1, 2)
55 years and above	1, IQR (1, 2)	Yes	1, IQR (1, 3)
Marital Status		**Blood**	
Not married	1, IQR (1, 2)	**Transfusion**	
Married	1, IQR (1, 2)	No	1, IQR (1, 2)
		Yes	1, IQR (1, 2)
Religion		**CVC**	
Christian	1, IQR (1, 1)	No	**2, IQR (1, 13**)
Non-Christian	1, IQR (1, 2)	Yes	1, IQR (1, 2)
Education Level		**Comorbidities**	
Primary	1, IQR (1, 2)	No	1, IQR (1, 2)
Post-primary	1, IQR (1, 1)	Yes	1, IQR (1, 2)
Employment Status		**History of VTE**	
Unemployed	1, IQR (1, 2)	No	1, IQR (1, 2)
Employed	1, IQR (1, 2)	Yes	1, IQR (1, 3.5)
Type of VTE			
PE	1, IQR (1, 2)		
DVT	1, IQR (1, 2)		

KEY: IQR – Interquartile range, VTE – Venous thromboembolism

4.4 Prescribing Patterns for VTE

4.4.1 Drugs Initially Prescribed After VTE Diagnosis

Two hundred and forty patients were on monotherapy with anticoagulants including warfarin (n=144, 57.6%), enoxaparin (n=39, 15.6%), and heparin (n=13, 5.3%). Those on dual therapy mostly used warfarin and enoxaparin (n=20, 8.0%) or warfarin and heparin (n=5, 5.2%) (Figure 5)

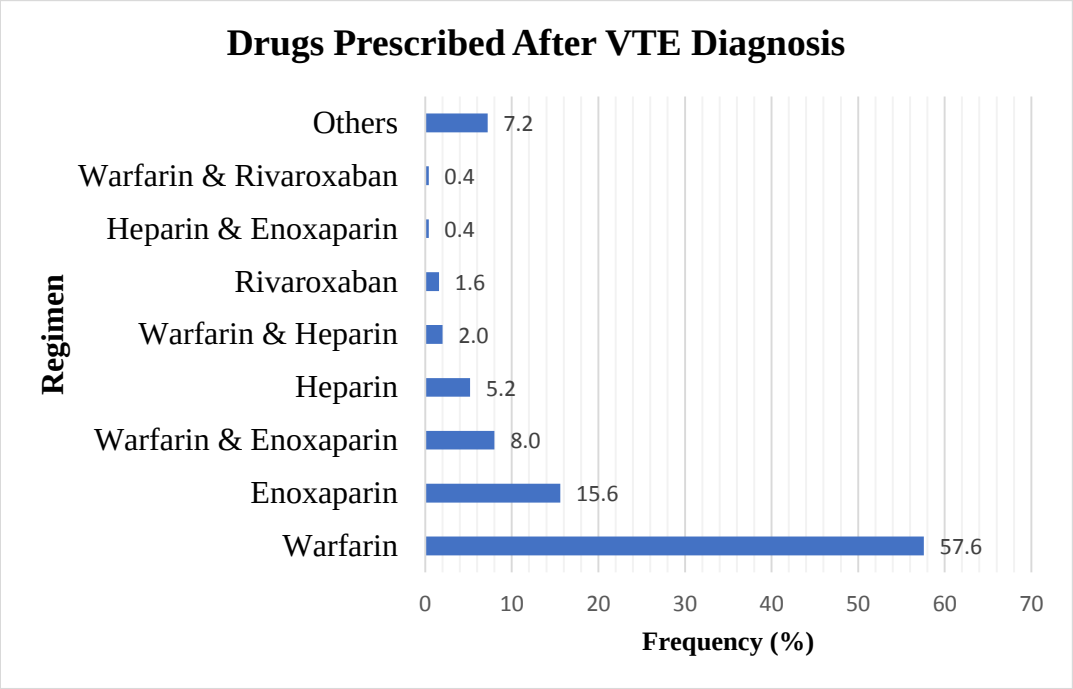

Fig 6: Drugs prescribed after VTE diagnosis

Others included dabigatran and apixaban.

4.4.2 Maintenance Therapy for VTE

The most common monotherapy regimen was with warfarin (n=182.0, 72.8%), enoxaparin (n=23, 9.2%), and rivaroxaban (n=6.0, 2.4%). Some patients were on dual therapy with warfarin and rivaroxaban (n=4, 1.6%).

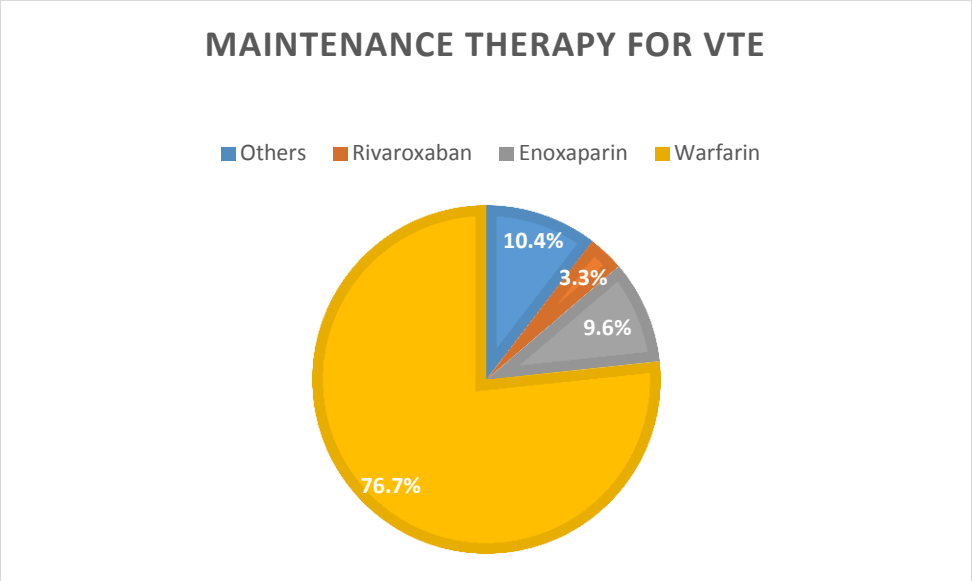

Fig 7: Maintenance therapy for VTE

Others included dabigatran and apixaban

4.4.3 Duration of VTE Treatment after Diagnosis

Most patients (n=182,72.8%) were treated for VTE for the first 3 months. Only a few patients (n=24, 9.6%) were being treated after twelve months. (Figure 7)

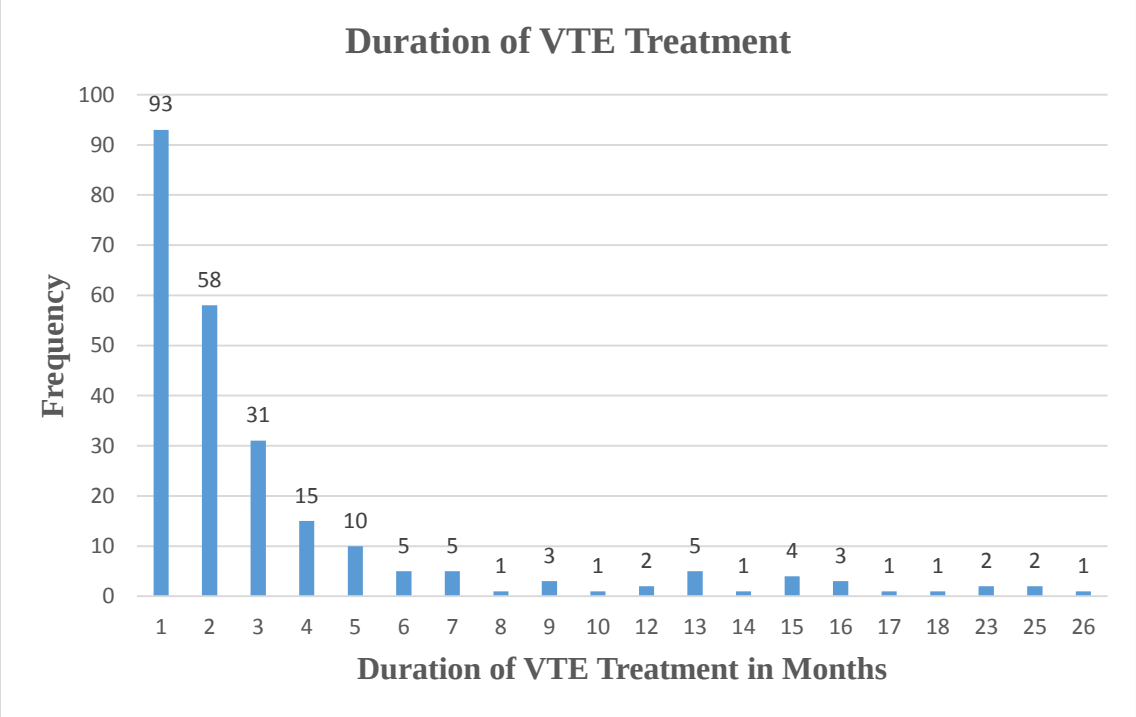

Figure 7: Duration of VTE Treatment

Table 4: Median Duration of VTE Treatment

Variable	Duration (Months) Median, IQR	Variable	Duration (Months) Median, IQR
Sex		**Alcohol Use**	
Male	2, IQR (1, 3)	No	2, IQR (1, 4)
Female	2, IQR (1, 5)	Yes	2, IQR (1, 4)
Age (Years)		**Tobacco Use**	
Less than 55 years	2, IQR (1, 3)	No	2, IQR (1, 4)
55 years and above	2, IQR (1, 4)	Yes	**2.5, IQR (1, 4.5)**
Marital Status		**Blood Transfusion**	
Not married	2, IQR (1, 4)	No	2, IQR (1, 4)
Married	2, IQR (1, 4)	Yes	2, IQR (1, 3)
Religion		**Central Venous Catheter**	
Christian	1, IQR (1, 5)	No	**3, IQR (1, 7)**
Non-Christian	2, IQR (1, 4)	Yes	2, IQR (1, 4)
Education Level		**Comorbidities**	
Primary	2, IQR (1, 4)	No	2, IQR (1, 4)
Post-primary	2, IQR (1, 4)	Yes	2, IQR (1, 4)
Employment Status		**History of VTE**	
Unemployed	2, IQR (1, 3)	No	**2, IQR (1, 4)**
Employed	2, IQR (1, 4)	Yes	1.5, IQR (1, 3.5)
Type of VTE			
PE	2, IQR (1, 4)		
DVT	2, IQR (1, 3)		

Key: DVT – Deep venous thrombosis, IQR – Interquartile range PE –Pulmonary embolism.

Patients who had no history of central venous catheter (CVC) use were treated for a longer duration [median 3, IQR (1,7) months] for VTE than those who had a CVC. Patients who used tobacco were treated for a longer period [median 2.5, IQR (1, 4.5) months] compared to those not using tobacco. Additionally, patients who had no history of VTE were treated for a longer time [median 2, IQR (1, 4) months] than those who previously had VTE (Table 4).

4.5 Recurrence of DVT

Among the patients being treated with anticoagulants 14 patients had a recurrence either during treatment, after treatment or both. Among the 14 patients, 11 developed VTE during the active treatment. Majority of the participants (n=4 36.4%) had VTE recurrence within the first month (Figure 8). After stopping treatment, 11 patients developed VTE, and most of the VTE events (n=7, 63.6%) developed within the first month of stopping anticoagulants (Figure 9).

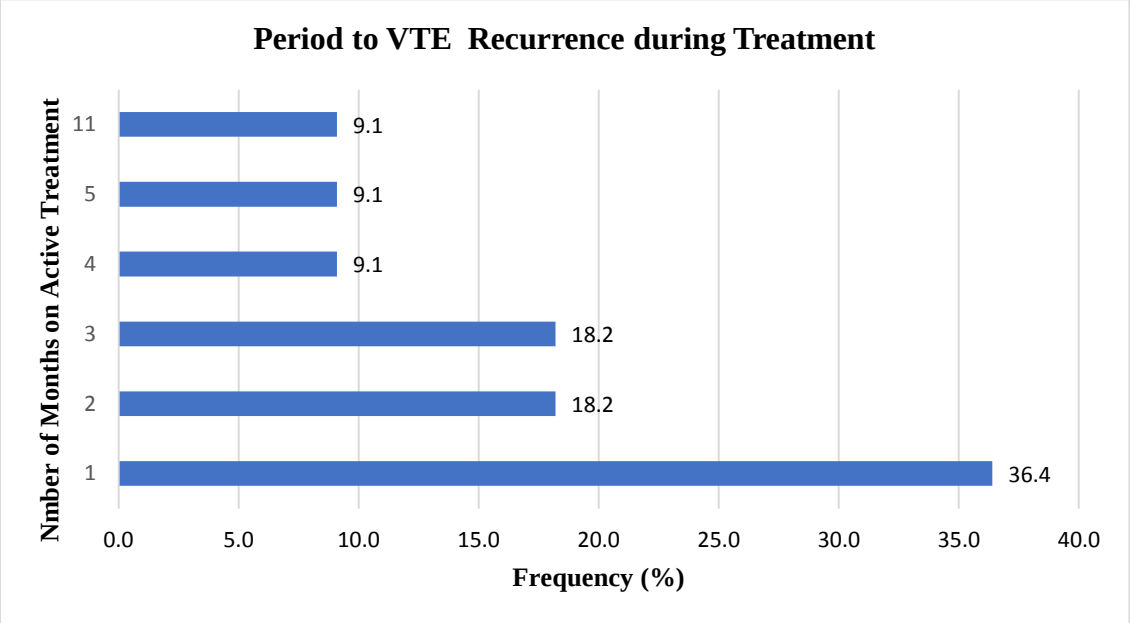

Fig 8: Proportion of patients and period to VTE Recurrence during treatment(Months)

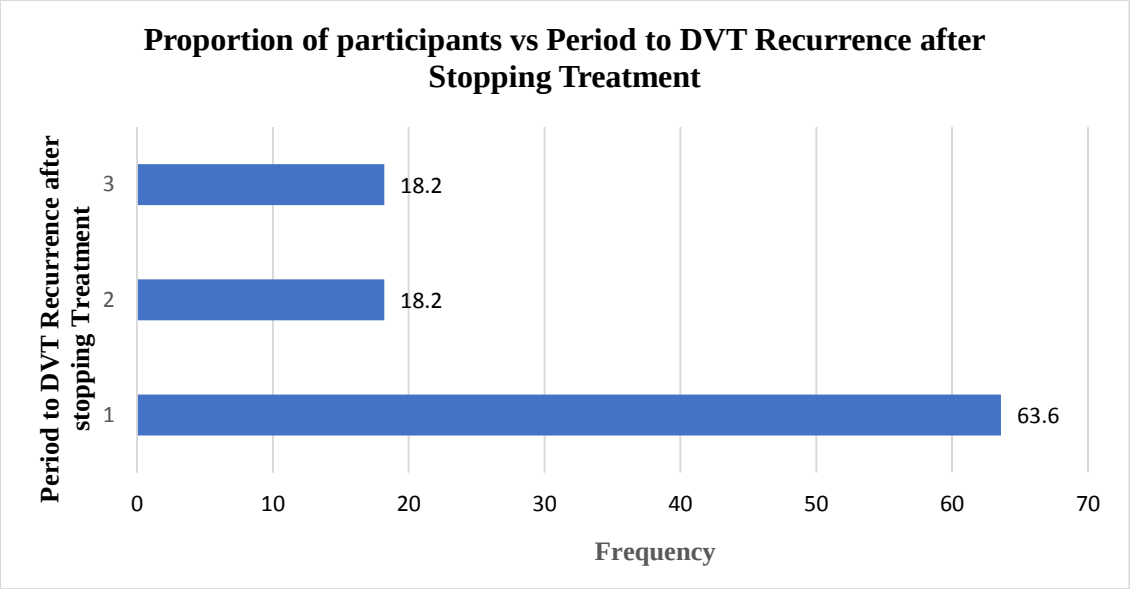

Fig 9: Proportion of patients and Period to VTE Recurrence After Stopping Treatment

4.6 Level of Anticoagulation Control among study participants

4.6.1 INR Values of study participants (N=199)

Among the 199 participants who had their INR values available, only 33 (16.6%) patients had the recommended INR in the range of 2-3. Most of the patients (n=139, 55.6%) had their INR below 2, while the rest (n=78, 31.2%) had an INR greater than 3.0 (Figure 10).

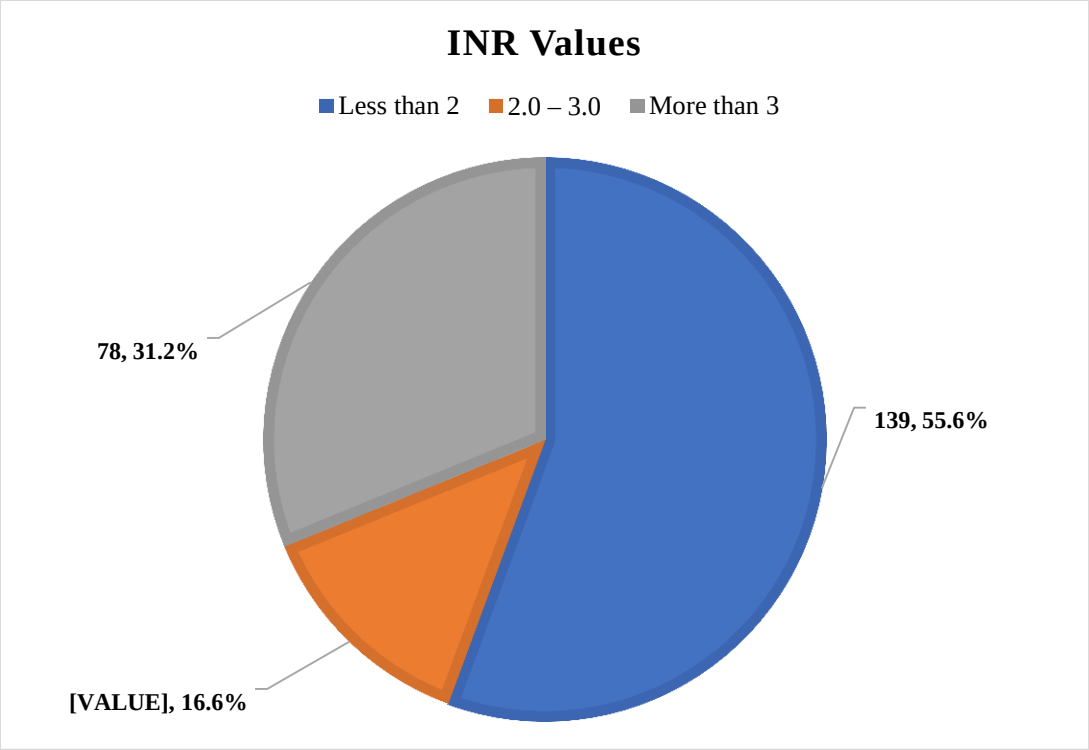

Fig 10: Proportion of patients with various INR Values

4.6.2 aPTT Values of study participants

Among the 133 patients whose aPTT values were recorded, 11 had their values within the recommended range for VTE prophylaxis (60-85 seconds) (Table 5).

Table 5: aPTT Values (N=133)

APTT VALUES (SECONDS)	**FREQUENCY (%) N=133**
LESS THAN 15	4 (3.03%)
15.0 - 30.9	42 (31.8%)
31.0 – 59.9	71 (53.8%)
60.0 - 80.0	**10 (7.6%)**
80.1 – 125.0	5 (3.8%)

Only one patient who was on dual anti-coagulants (warfarin and enoxaparin) had anti Xa level recorded. The patient had a value of 1.4 U/mL.

4.7 Occurrences of Major Bleeding Events

Forty-six patients (18.8%) of the patients had major bleeding events. Most had genitourinary (n=39, 84.8%) bleeding events. Other sites of bleeding included gastro-intestinal (n=4, 8.7%) and intracranial (n=6, 6.5%) bleeding (Figure 11).

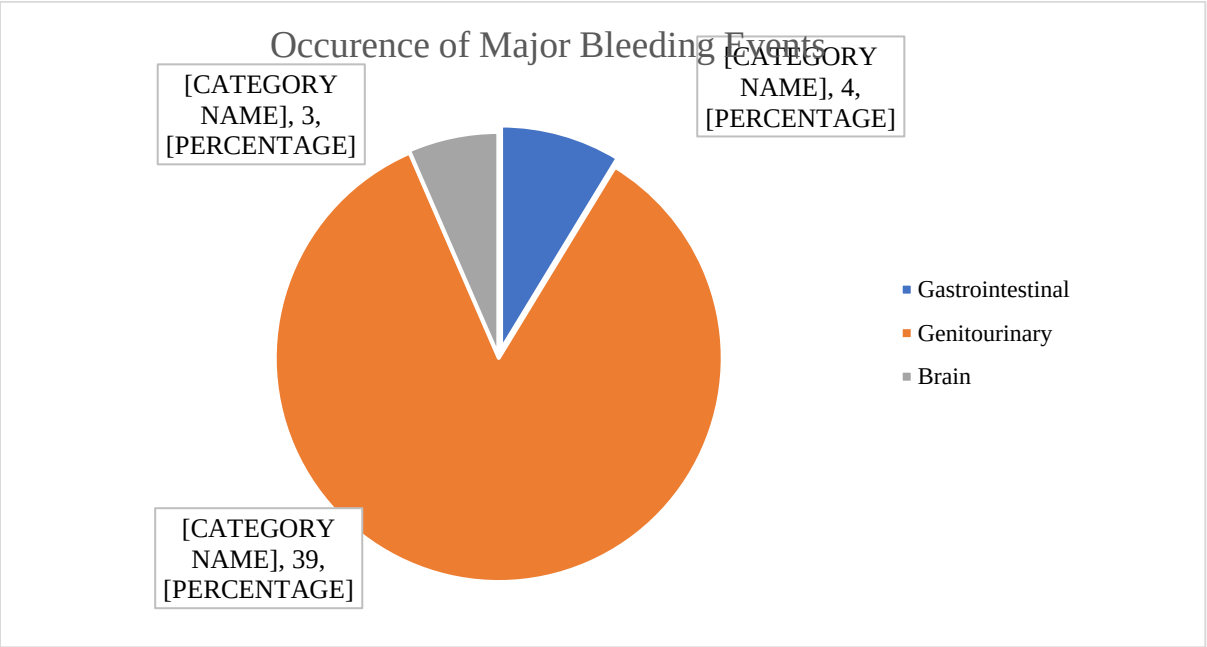

Fig 11: Occurrence of Major Bleeding Events

4.7.1 Occurrence of Major Bleeding Events according to Sociodemographic Characteristics

Most patients who were Christian (n=195, 78.0%), unemployed (n=170, 68.0%), non-smokers (n=187, 71.2%), and non-alcohol users (n=178, 71.2%) had no major bleeding events (Table 6).

Table 6: Occurrence of Major Bleeding Events according to Sociodemographic Characteristics

Occurrence of Major Bleeding (Frequency, n, %)		
Variable	**No**	**Yes**
Sex		
Male	59 (23.6%)	44 (17.6%)
Female	145 (58.0%)	2 (0.8%)
Age (Years)		
55 or less	109 (43.6%)	26 (10.4%)
More than 55 years	95 (38.0%)	20 (8.0%)
Marital Status		
Married	80 (32.0%)	15 (6.0%)
Not married	124 (49.6%)	31 (12.4%)
Religion		
Christian	**195 (78.0%)**	2 (0.8%)
Other religion	9 (3.6%)	44 (17.6%)
Education Level		
Primary	125 (50.0%)	22 (8.8%)
Post-primary	79 (31.6%)	24 (9.6%)
Employment Status		
Unemployed	**170 (68.0%)**	36 (14.4%)
Employed	34 (13.6%)	10 (4.0%)
Alcohol Use		
No	**178 (71.2%)**	45 (18.0%)
Yes	26 (10.4%)	1 (0.4%)
Tobacco Use		
No	**187 (74.8%)**	46 (18.4%)
Yes	17 (6.8%)	0 (0)

4.8 Inferential Analysis

4.8.1 Association between patient characteristics and type of VTE

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patient's profile and the type of VTE at $P \leq 0.05$. There was no significant relationship between the patients' profiles and the type of VTE (PE or DVT) (Table 7).

Table 7: Association between patient characteristics and the Type of Thromboembolism

Variable	Types of VTE		
	DVT	PE	P-value
Sex			
Male	179 (71.6%)	10 (4.0%)	0.207
Female	55 (22.0%)	6 (2.4%)	
Age (Years)			
≤55	128 (51.2%)	7 (2.8%)	0-395
56 – 74	103 (42.4%)	9 (3.6%)	
Marital Status			
Not married	88 (35.2%)	7 (2.8%)	0-624
Married	146 (58.4%)	9 (3.6%)	
Religion			
Non-Christian	11 (4.4%)	0 (0)	1.000
Christian	223 (89.2%)	16 (6.4%)	
Education Level			
Primary or less	139 (55.6%)	8 (3.2%)	0.460
Post-primary	95 (38.0%)	8 (3.2%)	
Employment Status			
Unemployed	191 (76.4%)	15 (6.0%)	0.218
Employed	43 (17.2%)	1 (0.4%)	
Alcohol Use			
No	208 (83.2%)	15 (6.0%)	1.000
Yes	26 (10.4%)	1 (0.4%)	
Tobacco Use			
No	217 (86.8%)	16 (6.4%)	0-610
Yes	17 (6.8%)	0 (0)	
Central Venous Catheter			
No	20 (8.0%)	3 (1.2%)	0.172
Yes	214 (85.6%)	13 (5.2%)	
Comorbidities			
None	125 (50.0%)	9 (3.6%)	0.826
Present	109 (43.6%)	7 (2.8%)	
History of surgery			
None	149 (59.6%)	13 (5.2%)	0.815
Present	85 (34.0%)	3 (1.2%)	
History of chemotherapy			
None	16 (6.4%)	1 (0.4%)	1.000
Present	218 (87.2%)	15 (6.0%)	
History of blood transfusion			
None	131 (52.4%)	12 (4.8%)	0.192
Present	103 (41.2%)	4 (1.6%)	
History of radiotherapy			
None	94 (37.6%)	8 (3.2%)	0.439
Present	140 (56.0%)	8 (3.2%)	
Patient dead			
No	172 (69.4%)	11 (4.4%)	0.636
Yes	60 (24.2%)	5 (2.0%)	

4.8.2 Association between patient characteristics and level of Anticoagulation

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patients' profiles and the INR levels at $P \leq 0.05$. There was a significant relationship between the INR level of the participants and being a Christian ($P=0.009$) (Table 8).

Table 8: Covariates of the Level of Anticoagulation

Variable	INR Levels			P-value
	<2.0	2.0 – 3.0	>3.0	
Sex				0.314
Male	100 (40.0%)	26 (10.4%)	63 (25.2%)	
Female	39 (15.6%)	7 (2.8%)	15 (6.0%)	
Age (Years)				0.271
≤55	71 (28.4%)	22 (8.8%)	42 (16.8%)	
56 – 74	68 (27.2%)	11 (4.4%)	36 (14.4%)	
Marital Status				0.199
Not married	46 (18.4%)	15 (6.0%)	34 (13.6%)	
Married	93 (37.2%)	18 (7.2%)	44 (17.6%)	
Religion				**0.009**
Non-Christian	2 (0.8%)	1 (0.4%)	8 (3.2%)	
Christian	137 (54.8%)	32 (12.8%)	70 (28.0%)	
Education Level				0.105
Primary or less	80 (32.0%)	15 (6.0%)	52 (20.8%)	
Post-primary	59 (23.6%)	18 (7.2%)	26 (10.4%)	
Employment Status				0.731
Unemployed	113 (45.2%)	29 (11.6%)	64 (25.6%)	
Employed	26 (10.4%)	4 (1.6%)	14 (5.6%)	
Alcohol Use				0.480
No	121 (48.4%)	31 (12.4%)	71 (28.4%)	
Yes	18 (702%)	2 (0.8%)	7 (2.8%)	
Tobacco Use				1.000
No	129 (51.6%)	31 (12.4%)	73 (29.2%)	
Yes	10 (4.0%)	2 (0.8%)	5 (2.0%)	
Central Venous Catheter				0.192
No	10 (4.0%)	2 (0.8%)	11 (4.4%)	
Yes	129 (51.6%)	31 (12.4%)	67 (26.8%)	
Comorbidities				
None	83 (33.2%)	17 (6.8%)	34 (13.6%)	0.071
Present	56 (22.4%)	16 (6.4%)	44 (17.6%)	
History of VTE				
None	117 (46.8%)	30 (12.0%)	71 (28.4%)	0.336
Present	22 (8.8%)	3 (1.2%)	7 (2.8%)	
History of surgery				
None	91 (36.4%)	17 (6.8%)	54 (21.6%)	0.197
Present	48 (19.2%)	16 (6.4%)	24 (9.6%)	
History of chemotherapy				
None	11 (4.4%)	2 (0.8%)	4 (1.6%)	0.725
Present	128 (51.2%)	31 (12.4%)	74 (29.6%)	
History of blood transfusion	83 (33.2%)	20 (8.0%)	40 (16.0%)	0.443
None	56 (22.4%)	13 (5.2%)	38 (15.2%)	
Present				
History of radiotherapy				
None	60 (24.0%)	14 (5.6%)	28 (11.2%)	0.567
Present	79 (31.6%)	19 (7.6%)	50 (20.0%)	
Type of VTE				
DVT	130 (52.0%)	33 (13.2%)	71 (28.4%)	0.217
PE	9 (3.6%)	0 (0)	7 (2.8%)	

4.8.3 Association between patient characteristics and VTE Recurrence

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patient's profile and the recurrence of VTE at P≤0.05. There was no significant relationship between the patients' profiles and the recurrence of VTE (Table 9).

Table 9: Association between Patient characteristics and VTE Recurrence(n=14)

Variable	Recurrence of VTE		P-value	Variable	Recurrence of VTE		P-value
	No	Yes			No	Yes	
Sex				**Central Venous Catheter**			
Male	177 (7134%)	10 (4.0%)	0.751	No	21 (8.5%)	1 (0.4%)	0.815
Female	57 (23.0)	4 (1.6%)		Yes	213 (85.9%)	13 (5.2%)	
Age (Years)				**Comorbidities**			
≤55	128 (51.6%)	6 (2.4%)	0.388	None	121 (48.8%)	11 (4.4%)	0.058
56 – 74	106 (42.7%)	8 (3.2%)		Present	113 (45.6%)	3 (1.2%)	
Marital Status				**History of surgery**			
Not married	89 (35.9%)	6 (2.4%)	0.718	None	152 (61.3%)	8 (3.2%)	0.553
Married	145 (58.5%)	8 (3.2%)		Present	82 (33.1%)	6 (2.4%)	
Religion				**History of chemotherapy**			
Non-Christian	9 (3.6%)	2 (0.8%)	0.122	None	17 (6.9%)	0 (0)	0.607
Christian	225 (90.7%)	12 (4.8%)		Present	217 (87.5%)	14 (5.7%)	
Education Level				**History of blood**			
Primary or less	136 (54.8%)	10 (1.0%)	0.409	**transfusion**	133 (53.6%)	9 (3.6%)	0.782
Post-primary	98 (39.5%)	4 (1.6%)		None	101 (40.7%)	5 (2.0%)	
				Present			
Employment Status				**History of radiotherapy**			
Unemployed	192 (77.4%)	13 (5.2%)	0.475	None	93 (37.5%)	9 (3.6%)	0.070
Employed	42 (16.9%)	1 (0.4%)		Present	141 (56.9%)	5 (2.0%)	
Alcohol Use				**Type of VTE**			
No	211 (85.1%)	11 (4.4%)	0.170	DVT	219 (88.3%)	13 (5.2%)	1.000
Yes	23 (9.3%)	3 (1.2%)		PE	15 (6.1%)	1 (0.4%)	
Tobacco Use				**Patient dead**			
No	220 (88.7%)	12 (4.8%)	0.225	No	169 (68.7%)	13 (8.3%)	0.123
Yes	14 (5.7%)	2 (0.8%)		Yes	63 (25.6%)	1 (0.4%)	
Warfarin				**Rivaroxaban**			
No	59 (23.8%)	1 (0.4%)	0.198	No	230 (92.7%)	14 (5.7%)	1.000
Yes	175 (70.6%)	13 (5.2%)		Yes	4 (1.6%)	0 (0)	
Enoxaparin							
No	211 (85.1%)	14(5.7%)	0.375				
Yes	23 (9.3%)	0 (0)					

4.8.4 Association between patient characteristics and adequacy of Anticoagulation

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patients' profiles and adequacy of anticoagulation at P≤0.05. There was a significant relationship between patients' mortality and having the ideal INR (P = 0.020) (Table 10).

Table 10: Association between patient characteristics and adequacy of anticoagulation INR (2.0-3.0)

Variable	Ideal INR		P-value	Variable	Ideal INR		P-value
	No	Yes			No	Yes	
Sex				**Central Venous Catheter**			
Male	163 (65.2%)	26(10.4%)	0.647	No	21 (8.4%)	2 (0.8%)	0.748
Female	54 (21.6%)	7 (2.8%)		Yes	196(78.4%)	31(12.4%)	
Age (Years)				**Comorbidities**			
≤55	113 (45.2%)	22 (8.8%)	0.117	None	117 (46.8%)	17 (6.8%)	0.797
56 – 74	104 (41.6%)	11 (4.4%)		Present	100 (40.0%)	16 (6.4%)	
Marital Status				**History of surgery**			
Not married	80 (32.0%)	15 (6.0%)	0.344	None	145 (58.0%)	17 (6.8%)	0.086
Married	137 (54.8%)	18 (7.2%)		Present	72 (28.8%)	16 (6.4%)	
Religion				**History of chemotherapy**			
Non-Christian	10 (4.0%)	1 (0.4%)	1.000	None	15 (6.0%)	2 (0.8%)	1.000
Christian	207 (82.8%)	32(12.8%)		Present	202 (80.8%)	31(12.4%)	
Education Level				**History of blood**			
Primary or less	132 (52.8%)	15 (6.0%)	0.09	**transfusion**	123 (49.2%)	20 (8.0%)	0.671
Post-primary	85 (34.0%)	18 (7.2%)		None	94 (37.6%)	13 (5.2%)	
				Present			
Employment Status				**History of radiotherapy**			
Unemployed	177 (70.8%)	29(11.6%)	0.468	None	88 (35.2%)	14 (5.6%)	0.839
Employed	40 (16.0%)	4 (1.6%)		Present	129 (51.6%)	19 (7.6%)	
Alcohol Use				**Type of VTE**			
No	192 (76.8%)	31(12.4%)	0.547	DVT	201 (80.4%)	33(13.2%)	0.140
Yes	25 (10.0%)	2 (0.8%)		PE	16 (6.4%)	0 (0)	
Tobacco Use				**Patient dead**			
No	202 (80.8%)	3 (12.4%)	0.856	No	154 (62.1%)	29(11.7%)	**0.020**
Yes	15 (6.0%)	2 (0.8%)		Yes	62 (25.0%)	3 (1.2%)	

4.8.5 Association between patient characteristics and having an Ideal aPTT

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patient's profile and having an ideal aPTT at P≤0.05. There was a significant relationship between having a history of surgery and an ideal aPTT (P = 0.036) (Table 11).

Table 11: Association between patient characteristics and having an ideal aPTT(60-80 seconds)

Variable	Ideal aPTT (60-80 seconds)		P-value	Variable	Ideal aPTT (60-80 seconds)		P-value
	No	Yes			No	Yes	
Sex				**CVC**			
Male	184 (73.6%)	5 (2.0%)	0.054	No	23 (9.2%)	0 (0)	0.612
Female	56 (22.4%)	5 (2.0%)		Yes	217 (86.8%)	10(4.0%)	
Age (Years)				**Comorbidities**			
≤55	131 (52.4%)	4 (1.6%)	0.520	None	129 (51.6%)	5 (2.0%)	0.816
56 – 74	109 (43.6%)	6 (2.4%)		Present	111 (44.4%)	5 (2.0%)	
Marital Status				**History of surgery**			
Not married	92 (36.8%)	3 (1.2%)	0.746	None	159 (63.6%)	3 (1.2%)	**0.036**
Married	148 (59.2%)	7 (2.8%)		Present	81 (32.4%)	7 (2.8%)	
Religion				**History of**			
Non-Christian	10 (4.0%)	1 (0.4%)	0.368	**chemotherapy**			
Christian	230 (92.0%)	9 (3.6%)		None	16 (6.4%)	1 (0.4%)	0.512
				Present	224 (89.6%)	9 (3.6%)	
Education Level				**History of blood**			
Primary or less	142 (56.8%)	5 (2.0%)	0.564	**transfusion**			
Post-primary	98 (39.2%)	5 (2.0%)		None	137 (54.8%)	6 (2.4%)	1.000
				Present	103 (41.2%)	4 (1.6%)	
Employment Status				**History of radiotherapy**			
Unemployed	198 (79.2%)	8 (3.2%)	0.690	None			
Employed	42 (16.8%)	2 (0.8%)		Present	100 (40.0%)	2 (0.8%)	0.207
					140 (56.0%)	8 (3.2%)	
Alcohol Use				**Type of VTE**			
No	216 (86.4%)	7 (2.8%)	0.081	DVT	224 (89.6%)	10(4.0%)	1.000
Yes	24 (9.6%)	3 (1.2%)		PE	6 (6.4%)	0 (0)	
Tobacco Use				**Patient dead**			
No	15 (6.0%)	8 (0.8%)	0.142	No	174 (70.2%)	9 (3.6%)	0.462
Yes	240 (96.0%)	10(4.0%)		Yes	64 (25.8%)	1 (0.4%)	

4.8.6 Association between patient characteristics and major bleeding episodes

A Pearson's Chi-Square test or Fischer's test was done to find the association between the patient's profile and the occurrence of major bleeding events $P \leq 0.05$. There was a significant relationship between occurrence of major bleeding events and the gender ($P < 0.001$), alcohol use ($P = 0.037$), tobacco use ($P = 0.048$), comorbidities ($P<0.001$), history of surgery ($P<0.001$), history of chemotherapy ($P = 0.043$), history of blood transfusion ($P=0.016$), history of radiotherapy ($P<0.001$), the type of VTE ($P=0.049$) and using rivaroxaban ($P = 0.045$) (Table 12).

Table 12: Association between patient characteristics and Major Bleeding Episodes (n=46)

Variable	Occurrence of Major Bleeding		P-value	Variable	Occurrence of Major Bleeding		P-value
	No	Yes			No	Yes	
Sex				**Comorbidities**			
Male	145(58.0%)	44(17.6%)	**<0.001**	None	121(48.4%)	13(5.2%)	**<0.001**
Female	59 (23.6%)	2 (0.8%)		Present	83 (33.2%)	33(13.2%)	
Age (Years)				**History of surgery**			
≤55	109(43.6%)	26(10.4%)	0.704	None	146(58.4%)	16 (6.4%)	**<0.001**
56 – 74	95 (38.0)	20 (8.0%)		Present	58 (23.2%)	30(12.0%)	
Marital Status				**History of chemotherapy**			
Not married	80 (32.0%)	15 (6.0%)	0.404	None	17 (6.8%)	0 (0)	**0.043**
Married	124(49.6%)	31(12.4%)		Present	187(74.8%)	46(18.4%)	
Religion				**History of blood transfusion**			
Non-Christian	9 (3.6%)	2 (0.8%)	1.000	None	124(49.6%)	19 (7.6%)	**0.016**
Christian	195(78.0%)	44(17.6%)		Present	80 (32.0%)	27(18.4%)	
Education Level				**History of radiotherapy**			
Primary or less	125(50.0%)	22 (8.8%)	0.904	None	97 (38.8%)	5 (2.0%)	**<0.001**
Post-primary	79 (31.6%)	24 (9.6%)		Present	107(42.8%)	41(16.4%)	
Employment Status				**Type of VTE**			
Unemployed	170(68.0%)	36(14.4%)	0.414	DVT	188(75.2%)	46(18.4%)	**0.049**
Employed	34 (13.6%)	10 (4.0%)		PE	16 (6.4%)	0 (0)	
Alcohol Use				**Patient dead**			
No	178(71.2%)	45(18.0%)	**0.037**	No	152(61.3%)	31(12.5%)	0.409
Yes	26 (10.4%)	1 (0.40%)		Yes	51 (20.6%)	14 (5.7%)	
Tobacco Use				**Warfarin**			
No	187(74.8%)	46(18.4%)	**0.048**	No	45 (18.0%)	16 (6.4%)	0.070
Yes	17 (6.8%)	0 (0)		Yes	159(63.6%)	30(12.0%)	
Central Venous Catheter	22 (8.8%)	1 (0.4%)	0.068	**Enoxaparin**			
No	182(72.8%)	45(18.0%)		No	186(74.4%)	41(16.4%)	0.585
Yes				Yes	18 (7.2%)	5 (2.0%)	

4.9 Bivariate and Multivariate Analysis

4.9.1 Independent predictors of major bleeding events

A bivariate and multivariate logistic regression was done to establish whether there was any significant association between the patient's profile and the occurrence of major bleeding events (Table 13). The bivariate regression revealed that there was a significant association between the occurrence of major bleeding events and gender (COR = 0.11, 95%CI: 0.03-0.48, p =0.003), comorbidities (COR = 3.70,95% CI: 1.84-7.45, p<0.001), history of surgery (COR = 4.72, 95% CI: 2.39-9.3, p<0.001), history of blood transfusion (COR = 2.20, 95% CI: 2.39-9.30, p = 0.017) and history of radiotherapy (COR = 7.43,95% CI: 2.82-19.57, p <0.001) (Table 12). The multivariate analysis showed that there was a significant relationship between the occurrence of major bleeding events and comorbidities (A.O.R = 3.91; 95%CI: 1.77- 8.63; p=0.001), gender (AOR=0.09; 95%CI;0.02-0.04; p=0.02), history of surgery (AOR = 4.5; 95%CI: 2.10-9.75; p <0.001) and history of radiotherapy (AOR = 6.13;95% CI: 2.19-17.23; p =0.001).

Table 13: Independent Predictors of Major Bleeding Events

Variable	Bivariate Analysis		Multivariate Analysis	
	Crude Odds Ratio (95% CI)	P-Value	Adjusted Odds Ratio (95% CI)	P-Value
Sex				
Male (Reference)	0.11	**0.003**	0.09	**0.02**
Female	(0.03 – 0.48)		(0.02 -0.40)	
Age (Years)				
≤55 (Reference)	0.88		-	-
56 – 74	(0.46 – 1.68)	0.704		
Marital Status				
Not married (Reference)	1.33	0.405	-	-
Married	(0.68 – 2.63)			
Religion				
Non-Christian (Reference)	1.01	0.985	-	-
Christian	(0.211 – 4.86)			
Education Level				
Primary or less (Reference)	1.72	0.096	-	-
Post-primary	(0.907 – 3.28)			
Employment Status				
Unemployed (Reference)	1.39	0.416	-	-
Employed	(0.63 – 3.06)			
Alcohol Use				
No (Reference)	0.15	0.068	-	-
Yes	(0.20 – 1.15)			
Central Venous Catheter				
No (Reference)	5.44	0.102	-	-
Yes	(0.71 – 41.43)			
Comorbidities				
None (Reference)	3.70	**<0.001**	3.91	**0.001**
Present	(1.84 – 7.45)		(1.77– 8.63)	
History of surgery				
None (Reference)	4.72	**<0.001**	4.5	**<0.001**
Present	(2.39 – 9.30)		(2.10 – 9.75)	
History of blood transfusion				
None (Reference)	2.20	**0.017**	-	-
Present	(1.14 – 4.22)			
History of radiotherapy				
None (Reference)	7.43	**<0.001**	6.13	**0.001**
Present	(2.82 – 19.57)		(2.19 – 17.23)	
Patient dead				
No (Reference)	1.35	0.410		
Yes	(0.66 – 2.73)			

4.9.2 Independent predictors of VTE Recurrence

A regression analysis of the patient's profile and having the VTE recurrence values was done at P≤0.05 to establish association. No independent predictors were identified.

Table 14: Covariates of Recurrence among study Participants

Variable	COR	p-value	Variable	COR	p-value
Sex			**Central Venous**		
Male	1.242	0.723	**Catheter**		0.815
Female	(0.375 – 4.113)		No	1.282	
			Yes	(0.160 – 10.288)	
Age (Years)	1.610		**Comorbidities**		
≤55	(0.542 – 4.786)	0.391	None	0.436	0.170
56 – 74			Present	(0.133 – 1.429)	
Marital Status	0.804		**History of surgery**		
Not married	(0.270 – 2.392)	0.695	None	1.390	0.554
Married			Present	(0.466 – 4.143)	
Religion	0.240		**History of blood**		
Non-Christian	(0.047 – 1.234)	0.088	**transfusion**		0.586
Christian			None	0.732	
	0.555		Present	(0.238 – 2.250)	
Education Level	(0.169 – 1.821)		**History of**		
Primary or less		0.332	**radiotherapy**		0.080
Post-primary	0.352		None	0.366	
	(0..45 – 2.762)		Present	(0.119 – 1.128)	
Employment Status			**Type of VTE**		
Unemployed	2.502	0.320	DVT	1.118	0.917
Employed	(0.650)		PE	(0.127 – 9.131)	
Alcohol Use			**Patient dead**		
No	2.619	0.182	No	0.206	0.132
Yes	(0.533 – 12.862)		Yes	(0.026 – 1.610)	
Tobacco Use					
No		0.236			
Yes					

4.9.3 Independent Predictors of an Ideal INR

A regression analysis of the patient's profile and having the ideal INR values was done at P≤0.05 to establish association. Patients who had died had 0.26 odds of having an ideal INR compared to

those who were alive (P=0.031). Multivariate analysis did not yield any significant predictors for INR.

Table 15: Covariates of an Ideal INR

Variable	COR	p-value	Variable	COR	p-value
Sex			**CVC**		
Male	0.850	0.722	No	1.599	0.540
Female	(0.348 – 2.076)		Yes	(0.357 – 7.169)	
Age (Years)			**Comorbidities**		
≤55	0.574	0.161	None	0.885	0.748
56 – 74	(0.264 – 1.248)		Present	(0.419 – 1.868)	
Marital Status			**History of surgery**		
Not married	0.864	0.705	None	2.028	0.064
Married	(0.405 – 1.842)		Present	(0.960 – 4.285)	
Religion			**History of chemotherapy**		
Non-Christian	1.490	0.708	None	0.990	0.985
Christian	(0.184 – 12.049)		Present	(0.322 – 3.040)	
Education Level			**History of blood transfusion**		
Primary or less	1.740	0.146	None		
Post-primary	(0.825 – 3.666)		Present	0.903	0.790
Employment Status			**History of radiotherapy**	(0.424 – 1.920)	
Unemployed	0.636	0.421	None		0.983
Employed	(0.211 – 1.914)		Present	1.008	
Alcohol Use			**Patient dead**	(0.474)	
No	0.515	0.382	No		**0.031**
Yes	(0.116 – 2.285)		Yes		
Tobacco Use				0.260	
No	0.902	0.895		(0.076)	
Yes	(0.196 – 4.143)				

4.9.4 Independent Predictors of an ideal aPTT

A regression analysis of the patient's profile and having the ideal aPTT values was done at P≤0.05 to establish association. Having a history of surgery increased the odds of having an ideal aPTT by 4.58 times (P=0.031). A backward stepwise regression analysis model did not yield any significant predictors for aPTT.

Table 16: Covariates of an ideal aPTT(60-80seconds)

Variable	COR	p-value	Variable	COR	p-value
Sex			**Tobacco Use**		
Male	3.286	0.067	No	3.750	0.113
Female	(0.918 – 11.761)		Yes	(0.731 – 19.241)	
Age (Years)			**Comorbidities**		
≤55	1.803	0.371	None	0.762	0.680
56 – 74	(0.496 – 6.552))		Present	(0.210 – 2.769)	
Marital Status			**History of surgery**		
Not married	1.425	0.614	None	4.580	**0.031**
Married	(0.359 – 5.650)		Present	(1.154 – 18.183)	
Religion			**History of blood transfusion**		
Non-Christian	0.391	0.395	None		
Christian	(0.045 – 3.396)		Present	0.887	0.855
Education Level			**History of radiotherapy**	(0.244 – 3.224)	
Primary or less	1.449	0.566	None		0.190
Post-primary	(0.409 – 5.139)		Present	2.857	
Employment Status			**Patient dead**	(0.594 – 13.741)	
Unemployed	1.179	0.839	No		0.261
Employed	(0.241 – 5.750)		Yes	0.302	
Alcohol Use				(0.038 – 2.432)	
No		0.062			
Yes					
	3.857				
	(0-935 – 15.905				

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses the results of the present study with reference to existing literature. The first part discusses the characteristics of the study participants and compares them with those of participants in similar studies. Comparison of the results with findings from similar studies follows thereafter. This is followed by the conclusion and recommendations based on the key findings of the study.

5.2 Discussion

Majority of the patients included in the study had DVT, 234 (93.6%) while 16(6.4%) had PE. This was higher than the findings of another study by Streiff *et al*., where the prevalence of DVT was between 55-60%(42). It was also higher than the findings of another study done at KNH where the frequency of DVT among the patients with VTE in breast cancer was 70%(25). Although there were varying prevalence rates of VTEs probably due to differences in study methodologies and participants' selection, DVT was commonest across all the studies. Only 12.8% of the patients included in the study had a history of VTE. This is consistent with the results of the Hokusai and CLOT trials where the history of VTE among the participants was 10.7% and 11% ,respectively(30).

Majority of the patients (75.6%) were women. Studies have also revealed that in Kenya, females are more likely to seek health services than their male counterparts(50). Furthermore, the incidence of cancer in the local registry shows female predominance(51).

The most prevalent cancer was cervical cancer (30%). This may be attributed to the fact that in Kenya, the most prevalent cancers are cervical and breast cancer(52) and the study eligibility criteria included patients with malignancies.

Looking at how the study participants were distributed according to age reveals that majority of the patients were above age 56 years (115, 45.9%) with a mean of 54.4 years. Previous studies at KNH revealed majority of the patients were above 45 years while another one in Uganda patients were aged > 48 years (5,6). This is the findings differ from the findings of a study done in the USA which found that majority of patients (43.5%) had an advanced age of ≥ 65 years (3,4). This difference is probably due to the fact that more than half of the cancers presenting in the US

occur in adults aged ≥65 years (53). It is also important to note that according to the World Bank, life expectancy in high income countries which includes the USA is 80.2 years while that of lower middle income countries is 67.3 years. Kenya, which is low middle income country has a life expectancy of 61.6 years and this may explain the difference in proportion of patients at different age categories(54).

Most of the patients were Christians (95.6%) and had never used alcohol (89.2%) or tobacco (93.2%). In a study conducted at KNH looking at patients on warfarin, over 90% were Christians and a similar proportion had no history of alcohol or tobacco use(55).
Most of the patients (148,59.2%) included in this study had undergone radiotherapy. In a related study done in KNH on breast cancer, majority of patients(70%) had a history of radiotherapy(25). The difference observed in the proportions could be related to methodology where in the other study only breast cancer patients were being enrolled while the present study included all types of cancers.

Less than half (116,46.4%) of participants had comorbidities, the most common being anemia (26%) and hypertension (14.9%). This was different from results obtained in a USA study where infection(31.2%) was the most common comorbid condition, followed by anemia(28.3%) (16). However, the proportions of anemic patients in USA and the present study were similar suggesting that cancer patients across the studies are more likely to develop anemia owing to the disease itself or use of chemotherapy.

In this study platinum based regimens (cisplatin (13.6%), oxaliplatin (12.3%) and carboplatin (2.5%), combined made up 28.4% of the anticancer agents that were prescribed. Platinum compounds were perhaps the most common anticancers prescribed because they are the most commonly used agents in the treatment of cervical, breast and ovarian cancers (56). The three were the most common cancers in the present study. For the individual agents, the most commonly used anti-cancer agent was flutamide (24.7%), an antiandrogen used in the treatment of Prostate cancer which was the fourth most prevalent cancer encountered in the study. The major concern is that from previous studies, platinum based regimens have been shown to increase the risk for VTE development. For instance, a study that was looking at VTEs in

patients with advanced gastroesophageal cancer found the prevalence of VTE among patients on Oxaliplatin plus Cisplatin to be 22.7%. The other commonly used drugs apart from the anticancer agents included metoclopramide (28%) and ondansetron (18%) perhaps as antiemetic for prophylaxis and management of chemotherapy induced nausea and vomiting.

Most patients (71.8%) developed VTE within the first month of cancer diagnosis. Research has revealed that the risk of VTE is at its peak in the immediate period after diagnosis of malignancies(26). Most of the therapeutic interventions including surgery, chemotherapy and radiotherapy occur during these initial stages after cancer diagnosis and this may contribute to the increased risk during this period. For instance, in patients with transitional cell carcinoma undergoing chemotherapy, 77% developed VTEs during the first two cycles of therapy(26). Participants who had no central venous catheter (CVC) had a delayed onset [median 2, IQR (1,13) months] of development of VTE after being diagnosed with cancer compared to those with a CVC. This can be due to the fact that catheters increase the risk of developing VTEs(57). This explains why the patients who had no CVC had a delayed onset of VTE development.

Majority of the patients were on warfarin (144,57.6%) for the initial treatment and maintenance therapies of VTEs. The findings are similar to those found in two other studies in the USA where 47.7% and 50% of the patients were on warfarin treatment (5,12). In a related study done in KNH on breast cancer, 80% of the patients with VTE were being managed using warfarin(25). The predominant use of warfarin in VTE treatment in cancer is not in line with the guidelines for management of VTE in cancer which recommend the utilization of a LMWH over VKAs (58,12). VKAs are known to interact with many drugs and foods hence leading to fluctuations in INR(5). The preferential use of VKAs in this study may be attributed to the high cost of LMWH and their mode of administration as subcutaneous injection and hence not preferable for long-term VTE management(5).

Most of the patients in this study were on anticoagulation therapy for less than 3 months. This finding was similar to that of a study in the USA(41). However, the present study had a higher frequency (151, 60.9%) of participants on < 3months therapy than that of related study at 54.1% (41). These results are not consistent with treatment guidelines which recommend VTE treatment

duration to be 3-6 months. However, this study found that patients who had no history of CVC, no history of tobacco smoking and no history of previous VTE were treated for longer duration when compared to their counterparts who had these characteristics. This can be due to the fact that most of the patients with a CVC are usually admitted to the wards where they receive anticoagulants for the period which they are admitted which may not be longer than 3 months. Smoking has been linked to VTE development and this may explain the longer duration of anticoagulation(59).

In total 14 patients (5.6%) had recurrent VTE in the study. This was different from the results obtained in another study where the recurrence was 20.1% (41). This deviation may be attributed to the smaller sample size used in the current study hence the outcome may have been underestimated. The findings are also different from those of the CLOT and CATCH trials which were looking at recurrence of in patients receiving warfarin and LMWH which found the total recurrence rate of VTE among patients on treatment to be 13.4% and 8.8%, respectively (9,10). The CLOT trial had 672 patients while the CATCH trial had 900 patients hence the huge difference in VTE recurrence compared to this study. No significant association was established between the patients' profiles and VTE recurrence.

Majority of the patients who had a VTE recurrence (36.4%) developed it within the first month. After stopping anticoagulation treatment, 63.6% of the patients developed VTE within the first month. This is consistent with a study that showed some patients had recurrence within 0 to 3 months of active treatment and after halting anticoagulant therapy(41).

In this study 18.8% of the patients had major bleeding events. This was higher than the results obtained from a study in the USA which reported the frequency of major bleeding events at 12.2% (41). Another study found the bleeding events to be 8.5%(42). The higher frequency of bleeding in the current study may be due to the comorbid conditions which have been shown to increase risk of bleeding in VTE patients who are on anticoagulation therapy. This is consistent with literature that has found comorbidities to increase the risk of major bleeding events(60). Anemia, which was the most common comorbidity in our study, has been shown to increase the risk of major bleeding events among VTE patients who are being

anticoagulated(61).Furthermore, the identified correlates of major bleeding events were comorbidities gender , history of surgery and history of radiotherapy.Hypertension (14.9%), cerebrovascular accidents (2.6%), abnormal renal function (6.5%), CKD (3.2%) and labile INRs are some of the HAS-BLED score components that are associated with increased bleeding(60).It may also be partially explained by the fact that majority of the bleeding events were genitourinary (84.8%) which is a sign of cervical cancer which was the most prevalent malignancy in the current study.

The significant association between history of surgery and major bleeding events may be due to the bridging therapy that is given perioperatively. History of surgery may be associated with major bleeding events due to perioperative bridging anticoagulation which have been shown to increase the risk of bleeding(62). In a certain study, bridging anticoagulation increased the risk of major bleeding events(62). Radiotherapy was found to also have a significant association with occurrence of bleeding events. This is different from other studies which show radiotherapy as having a significant association with the development of VTE(25). This can be due to the fact that out of the 148 patients who had a history of radiotherapy, 50(33.8%) had an INR that was greater than 3 hence predisposing them to bleeding.

The current also found a significant relationship between gender and occurrence of major bleeding events. The male gender had an increased risk of occurrence of bleeding events. This differs with the findings of other studies which found the female gender to have a higher risk of occurrence of major bleeding events when on anticoagulation therapy(55). However, the findings of our study agree with the findings of some other two studies which found the male gender to have a higher occurrence of bleeding events during anticoagulation (63,64). The findings on gender and bleeding outcomes in this study can be due to the fact that majority of the patients who had an INR of greater than 3 were males suggesting that they were more likely to suffer bleeds. Out of the 46 patients who had major bleeding occurrences, 30 (65.2%) were being treated with warfarin. These results are higher than the findings of another study done in the US which found the frequency of bleeding events among the patients being treated with warfarin at 20.2% (41). Another study done at KNH by Nyamu *et al.* found the frequency of bleeding

among patients on warfarin to be 27.8%(55). These variations can be explained by differences in patient populations and the study methodologies.

Only 33(16.6%) of the patients had their INR in the recommended range of 2-3. This was different from the results of a related study done in KNH which found that only 27.5% of the patients on warfarin were adequately anticoagulated(37). This shows that there has been a deterioration over time. Furthermore, the variation on the proportions of adequately anticoagulated may be explained by the different study designs and periods. On univariate analysis there was a significant association between religion and mortality of the participants and having an ideal INR. However, these associations were lost on logistic regression analysis.
Only 10% of the patients had the recommended aPTT levels. A study done in KNH found that few (26.3%) surgical patients receive prophylaxis(67). This may explain low frequency of patients with ideal aPTT levels. On univariate analysis, there was a significant relationship between having a history of surgery and an ideal aPTT. However, on logistic regression analysis, this association was dropped.

This was an index study at KNH that sought to establish anticoagulant therapy outcomes among cancer patients with VTE. The study identified the medications used in the management of VTE in malignancies and also established the outcomes of anticoagulants used in the treatment of VTEs. The study also found statistically significant associations between the occurrence of major bleeding events and radiotherapy, comorbidities and surgery.

Due to the fact that the study conducted was a retrospective cross-sectional study, causal inference between various anticoagulants and the outcomes of treatment was limited. The study also assumed that all the medications prescribed to the patients were actually being taken by the patient which is not always the case. There is a possibility that there was an underestimation of the frequency of VTE recurrence due to underreporting of VTE events in the patient files.

Since the study looked at patient files, missing data such cancer staging and duration of anticoagulation for most patients was a big problem. Also some of the measurements used in the

study were done at different times and in different laboratories. Due to time limitations the study was retrospectively making follow up of the patients through the 5 years difficult.

5.3 Conclusion

Most cancer patients suffer from DVT as opposed to PE. Warfarin is the most used anticoagulant in the treatment of VTEs in cancer despite the guidelines recommending the use of LMWH in the treatment of malignancy associated VTE. There is poor anticoagulation control with majority of the patients being under-anticoagulated (INR <2). Most patients are being anticoagulated for a shorter period (1month or less) than the recommended 3-6 months or more. However, the frequency of recurrence of VTE among cancer patients is low.

The frequency of major bleeding events in cancer patients on anticoagulation therapy was high and majorly attributed to presence of comorbidities, gender, history of surgery and history of radiotherapy.

5.4 Recommendations

5.4.1: Recommendations for further research

There is emerging use of DOACs in the treatment of VTE in cancer patients. Therefore, a study should be done looking at the prescribing patterns of DOACs and their outcomes among cancer patients with VTE since only a small percentage of patients in this study were on DOACs.

A study looking at factors that are associated with inadequate levels of anticoagulation among cancer patients would give insight into why majority of patients were not adequately anticoagulated and also help in creating solutions.

A large prospective study to find out the outcomes of anticoagulation among cancer patients with VTE (VTE Recurrences rate, Bleeding events and death) should be conducted so as to establish their accurate incidence rates and their associated risk factors.

5.4.2 Recommendations for policy and practice

Since warfarin is the most used anticoagulant in this study and the level of anticoagulation among study participants was inadequate, measures should be put in place to ensure adequate levels of anticoagulation among these patients. Physicians should be sensitized on the guideline recommendations of duration of anticoagulation in cancer patients and encouraged to adhere to it.

To prevent the high frequency of bleeding events among patients on anticoagulants, they should be followed up more aggressively. A specialized pharmacist-led clinic that is focused solely on anticoagulation management will ensure that patients are followed up from a central place and the negative outcomes of anticoagulation are noted earlier or prevented.

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APPENDICES

Appendix 1: Eligibility screening form

1. Patient Information

Title	DETERMINANTS AND MANAGEMENT OF VENOUS THROMBOEMBOLIC DISORDERS AMONG CANCER PATIENTS AT KNH
KNH/UoN/ERC Protocol Number	
Investigator	Dr. Susan Nyabate Mageto

2.Participant Information

Participant ID:
Gender: Male ☐ Female ☐

3.Eligibility criteria

Inclusion criteria	Yes	No
Does the patient have cancer?		
Does the patient have VTE?		
Is the patient receiving anticoagulant therapy?		
Exclusion criteria		
Is the patient receiving prophylactic anticoagulants?		

4.Eligibility statement

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

Appendix 2: Questionnaire

DETERMINANTS AND MANAGEMENT OF VENOUS THROMBOEMBOLIC DISORDERS AMONG CANCER PATIENTS AT KNH

A: BIODATA

1.Patient number	
2.Name initials	
3.Address/ contact	
4.Study date	

B: SOCIAL DEMOGRAPHIC CHARACTERISTICS

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

6.Religion? 1.Christian ☐ 2. Muslim ☐ 3. Other…….

Employment status?

6. Marital status 1. Married ☐ 2. Single ☐ 3. Divorced ☐ 4. Widowed ☐ 5. Separated ☐

7. Education Level 1. Primary ☐ 2. Secondary ☐ 3. Tertiary ☐

8. Alcohol use? 1.Yes ☐ 2. No ☐

9. Tobacco use? 1.Yes ☐ 2. No ☐

C: DETERMINANTS OF VTE IN CANCER PATIENTS

10. Does the patient have any Comorbidities? 1.Yes ☐ 2. No ☐

11. If yes, what type of comorbidity?

☐ 1. CKD

☐ 2. Diabetes

☐ 3. Pulmonary disease

☐ 4. Obesity(BMI)

☐ 5. Atherothrombotic diseases

☐ 6. Hypertension

☐

7. HIV

☐ 8. Other comorbidities? …….

13. Does the patient have previous History of VTE? 1. Yes ☐ 2. No ☐

14. What kind of cancer treatment did the patient receive?

1.Surgery Yes ☐ No ☐

2.Chemotherapy Yes ☐ No ☐

3. Type of chemotherapeutic agents/ Regimen

……

……

……..

……...

……...

……

4. Anti-angiogenic agents 1. Bevacizumab 2. Lenalidomide 3. Everolimus 4. Other……

5.Hormonal therapy 1. Leuprolide 2. Gosarelin 3. Relugolix

4. Other…….

6. Blood transfusion 1. Yes ☐ 2. No ☐

7.Central venous catheter for delivery of drugs? 1. Yes ☐ 2. No ☐

8. Radiotherapy? 1. Yes ☐ 2. No ☐

15. Did the patient have the following biomarkers?

1. D-dimers level >250ng/ml, or >0.4mcg/ml: Specific level…….

2.C-reactive protein level >10mg/dl: Specific level…….

3.Platelet counts level >450,000 cells: Specific values……...

16. What Type of cancer did the patient have?

☐ 1.ALL

☐ 2.AML

☐ 3.Bladder

☐ 4. Bone cancer

☐ 5.Brain cancer

☐ 6.Breast
☐ 7.Cervical cancer
☐ 8.CML
☐ 9.Colon
☐ 10.Colorectal cancer
☐ 11.Esophageal cancer
☐ 12.Eye cancer
☐ 13.Gastric cancer
☐ 14.Head and neck cancer
☐ 15. Head and neck cancer
☐ 16. Hepatocellular cancer
☐ 17.Hodgkin's lymphoma
☐ 18. Kaposi's sarcoma
☐ 19.Kidney
☐ 20.Lung
☐ 21.Multiple Myeloma
☐ 22.Non-Hodgkin's lymphoma
☐ 23.Ovary
☐ 24.Pancreas
☐ 25.Penile cancer
☐ 26.Pituitary tumor
☐ 27.Prostate
☐ 28.Skin cancer
☐ 29.Testicular cancer
☐ 30.Uterus
☐ 31.Others (specify)

17. What stage of cancer is the patient in?

☐ 1.Stage i
☐ 2.Stage ii
☐ 3.Stage iii
☐ 4.Stage iv

☐ 5.Not staged

☐ 6.Other.....

18. How long after cancer diagnosis did the patient develop VTE?.....months

19. What type of VTE?

1. DVT ☐

2.PE ☐

D: MANAGEMENT OF VTE

20. What anticoagulant was used in the treatment of the VTE?

1.Initial management

☐ 1.Enoxaparin

☐ 2.Heparin

☐ 3. Rivaroxaban

☐ 4. Warfarin

☐ 5. Others?.....

2.Long-term management

☐ 1.Enoxaparin

☐ 2. Heparin

☐ 3.Rivaroxaban

☐ 4.Warfarin

☐ 5. Others?.....

21. What was the duration of VTE treatment? ----------months

E: OUTCOMES OF ANTICOAGULATION THERAPY

22. What were the outcomes of Anticoagulation therapy

☐ 1. Major Bleeding events?

1. Gastrointestinal?.....

2. Intracerebral?.....

3. Genitourinary?.....

4. Other?.....

☐ 2. Did the VTE recur? 1.Yes ☐ 2. No

☐ 3. If yes in 2, How long after initiation of anticoagulants?.....

☐ 4. If yes in 2, How long after stopping anticoagulant therapy?.....

☐ 5.Death……

23. What was the level of anticoagulation at the time of study?

Measuring parameter	Level
1.INR	
2.Antifactor Xa activity	
3.APTT	
4.PT	

Appendix 3. Dummy tables

Table 17: Sociodemographic features

Characteristic	Mean	Median
Age		
Height		
Weight		
BMI		

Table 18: Frequency of VTE among male and female cancer patients

Sex	Frequency	Proportion (%)
Male		
Female		
Total		

Table 19: Frequency distribution of VTE according to type of cancer

Cancer site/type	Frequency	Proportion
Prostate		
Breast		
Bladder		
Uterus		
Colon		
Lung		
Hodgkins lymphoma		
Non Hodgkins lymphoma		
Multiple myeloma		
AML		
ALL		
CML		
CLL		
Ovary		
Stomach		
Kidney		
Pancreas		
Other		
Total		

Table 20: Frequency of VTE according to treatment

Treatment	Frequency	Proportion
Surgery		
Radiology		
Chemotherapy		
Anti-angiogenic therapy		
Erythropoiesis stimulating agents		
Blood transfusions		
Total		

Table 21: Outcomes of anticoagulation with warfarin

Warfarin		
Outcome	Frequency	Proportion
Recurrence		
Bleeding Event		
Mortality		
Total		

Table 22: Independent predictors of developing VTE

Variables	Bivariate	Multivariate

Appendix 4: ERC Approval Letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Full Access to Records Code 4020 511

Ref: KNH-ERC/A/151

30th April 2021

Dr. Susan Nyabate Mageto
Reg. No.U56/34437/2019
Dept of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL * APPROVED 30 APR 2021 KNH/UoN-ERC P.O. BOX 20723-00202 NAIROBI

Dear Dr. Mageto

RESEARCH PROPOSAL –DETERMINANTS AND MANAGEMENT OF VENOUS THROMBOEMBOLIC DISORDERS AMONG CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL (P83/02/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 30th April 2021 – 29th April 2022.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study.

Protect to discover

Appendix 5: KNH Study Registration Certificate

KNH R&P FORM 01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2710555
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   Dr. Susan Nyabate Mageto
2. Email address: susanmagete.mageto@gmail.com Tel. No. 0715823203
3. Contact person (if different from PI).....
4. Email address: ..... Tel. No. .....
5. Study Title
   Determinants and management of Vesico Thrombotic disease among ovarian cancer patients
6. Department where the study will be conducted CTC
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted:
   Name: DD C. Mjonjesa Signature [signature] Date 17/5/21
8. KNH UoN Ethics Research Committee approved study number P83/02/2021
   (Please attach copy of ERC approval)
9. I Dr. Susan Nyabate Mageto commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature [signature] Date 13th May 2021
10. Study Registration number (Dept/Number/Year) CTC 110 / 2021
    (To be completed by Medical Research Department)
11. Research and Program Stamp KENYATTA NATIONAL HOSPITAL Research & Programs 19 MAY 2021

All studies conducted at Kenyatta National Hospital must be registered with the Department of Medical Research and investigators must commit to share results with the hospital.

17th Nov. 2021

Appendix 6: Plagiarism Report

MANAGEMENT AND OUTCOME OF VENOUS THROMBOEMBOLIC DISORDERS AMONG CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

10%	7%	6%	1%
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