PREVALENCE, RISK FACTORS AND INTERVENTIONAL STRATEGIES FOR MANAGEMENT OF THROMBOCYTOPENIA AMONG ADULT PATIENTS TREATED FOR CANCER AT KENYATTA NATIONAL HOSPITAL

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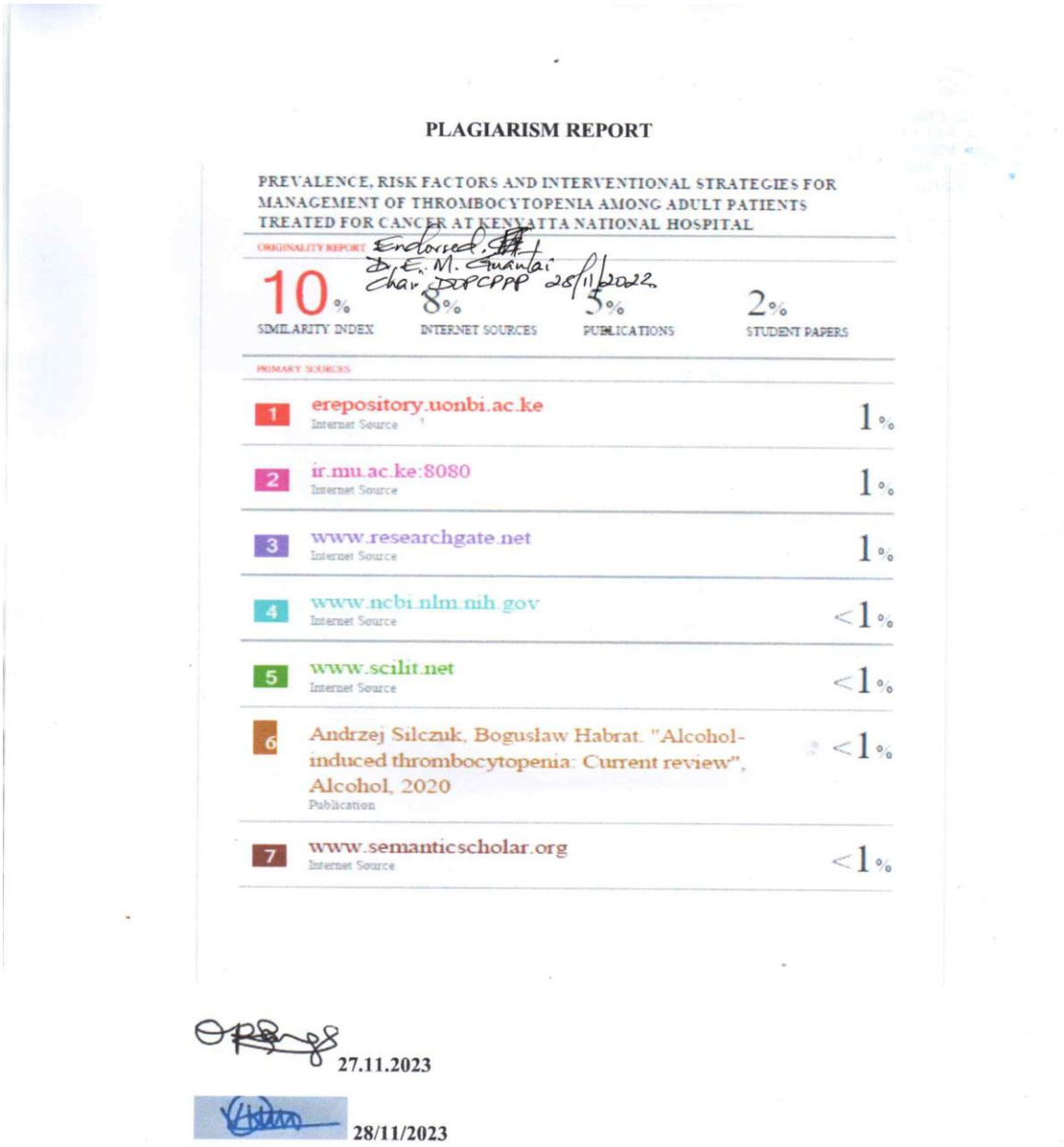

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APPROVAL BY SUPERVISORS

This dissertation has been submitted for review and examination for the award of degree with our approval as university supervisors.

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DEDICATION

To my dear wife, Diana Nungari and my daughters, Meghan and Meline for their unending love, support and encouragement throughout this program

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I would like to thank the almighty God who has enabled me to reach this far.

My sincere gratitude goes to my project supervisors Dr. Sylvia Opanga and Professor Faith Okalebo for their invaluable guidance and assistance throughout the course of this project.

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LIST OF ABBREVIATIONS

ALL	Acute lymphocytic leukemia
AML	Acute myelogenous leukemia
APS	Antiphospholipid syndrome
ARDS	Acute respiratory distress syndrome
BMS	Bone Marrow Suppression
CIT	Chemotherapy induced thrombocytopenia
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
CTD	Connective tissue diseases
DIC	Disseminated Intravascular Coagulation
DITP	Drug-Induced Immune Thrombocytopenia
EBV	Epstein-Barr Virus
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDAC	Histone Deacetylase
HELLP	Hemolysis, Elevated liver enzymes, Low platelet count
HIV	Human Immunodeficiency Virus
HL	Hodgkin’s Lymphoma
HUS	Hemolytic Uremic Syndrome
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
KHN	Kenyatta National Hospital
MDS	Myelodysplatic syndrome
NHL	Non-Hodgkin's lymphoma
NSCLC	non-small cell lung cancer
PNH	Paroxysmal nocturnal hemoglobinuria
RBC	Red blood cells
RDI	Relative Dose Intensity
TCP	Thrombocytopenia
TTP	Thrombotic Thrombocytopenia Purpura
USA	United States of America

OPERATIONAL DEFINITIONS

Chemotherapy induced thrombocytopenia is a disorder that that develops due to the toxic effect of chemotherapy agents on platelet-forming cells in the bone marrow resulting in low platelet counts.

Cytopenia is a condition in which there is a lower-than-normal number of blood cells.

Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets

Relative dose intensity is defined as the quantity of chemotherapy given over a given time in relation to the standard dosage.

Thrombocytopenia is the deficiency of platelets in blood which can lead to bleeding and easy bruising.

ABSTRACT

Introduction: Thrombocytopenia is a usual complication in patients with cancer. Cancer drugs and the underlying disease processes are the most frequent causes of thrombocytopenia which can lead to dose modifications or delays. These interferences can result in poorer survival and disease progression. Limited data exist on the characteristics of cancer patients at risk of thrombocytopenia.

Objective: This study sought to identify the prevalence and risks factors associated with thrombocytopenia in patients on cancer treatment and its interventional strategies.

Methods: The study was conducted after being granted approval by KNH/UoN-ERC, KNH Research and Programs department and oncology department. This was a cross sectional study involving 137 participants who were above 18 years and initiated on cancer treatment between January 2019 and June 2022 at Kenyatta National Hospital-Cancer Treatment Center. They were selected by clustering the study population into hematological and solid malignancies, and then systematic sampling was done on each cluster. Data were abstracted from the participants' files using a predesigned tool. Data were analyzed using STATA statistical software version 13. Descriptive data analysis was carried out, with categorical variables summarized by percentages and frequencies. Continuous data was summarized by median and interquartile range. Logistic regression was conducted to determine association between independent variables and the outcome variable.

Results: More than half 93(67.9%) of the participants were female. Majority 51 (37.2%) were above 60 years. The median age was 52 years (IQR=25, 79). Solid cancers were the most prevalent at 108 (79%). Breast cancer was the most common type of cancer among the participants 39(28.9%), followed by cervical cancer 23(16.8%), esophageal cancer 14(10.2%) and multiple myeloma 14(10.2%). Most of the participants were in cancer stage IV 48(35.6%). Liver disease was the most preponderant comorbidity 22(16.1%) followed by kidney disease 16(11.8%). Doxorubicin and cyclophosphamide was the commonly used chemotherapeutic combination 13(9.5%) followed by cisplatin and paclitaxel combination 12(8.8%). The prevalence of thrombocytopenia in this study was

43(31.4%) with majority having mild thrombocytopenia. There was no intervention instituted for participants with mild thrombocytopenia whereas platelet transfusion was the main intervention for those with severe thrombocytopenia. Participants with hematological malignancies had 0.02 times the odds of having thrombocytopenia compared to those with solid malignancies (OR=0.025, 95% CI 0.005, 0.129 p<0.001). Participants on carboplatin based regimens have 0.06 times the odds of having the thrombocytopenia as compared to the participants on the other regimens (OR=0.007, 95% CI 0.005, 0.577 p=0.015).

Conclusion: The results suggest that thrombocytopenia in cancer patients at KNH is a relevant problem in clinical practice. The observed prevalence of thrombocytopenia was comparable with that observed in a recent Indian and Ugandan studies. Platelets transfusion was the main intervention for participants with severe thrombocytopenia.

CHAPTER ONE: INTRODUCTION

1.1 Background

Worldwide, cancer accounts for nearly 10 million deaths annually(1)**.** It is among the main causes of death in Kenya, with leading cancers being breast, cervical, prostate, esophageal, and colorectal(2). Cancer and its treatment are risk factors for hematologic toxicity. Cytopenia, which is a decrease in all the three blood cell lines leads to anemia, neutropenia and thrombocytopenia, and is a major problem in cancer treatment(3).

Thrombocytopenia (TCP) is a low platelet count in blood, less than 150,000/µL in adults. Severity of TCP is classified into mild (100,000-150,000/µL platelets), moderate (50,000-99,000/µL platelets), and severe (<50,000/µL platelets). Severe thrombocytopenia causes a high risk of bleeding and is an indication needing treatment. Platelet transfusions can be given either for prevention or treatment(4). Thrombocytopenia is a consequence of reduced platelet production, raised utilization, or sequestration(5).

Thrombocytopenia is a common complication of cancer and its treatment (6). Besides causing increased risk of bleeding, it restricts chemotherapy dose and frequency. There are many causes of TCP in cancer patients, with cytotoxic chemotherapy being the most recurrent one. Others include infiltration of cancer into bone marrow and spleen, infection, disseminated intravascular coagulation, medications (which include quinine, vancomycin, carbamazepine and heparin), thrombotic thrombocytopenic purpura and radiation(7). Thrombocytopenia can be experienced in patients with different types of cancers as a result of the disease or its treatment(8).

Thrombocytopenia in cancer patients is a risk factor for compromised management and suboptimal outcomes with substantial cost of care(9). The present research seeks to identify the risk factors for thrombocytopenia in patients on cytotoxic chemotherapy, which can aid in recognizing high risk patients to institute early interventions.

1.2 Statement of the problem

Approximately 300,000 people per year globally receive cycles of cancer treatment associated with notable thrombocytopenia(10). A study in Uganda on patients with hematological malignancies undergoing chemotherapy reported thrombocytopenia in 58% of patients and 18% of those had clinically significant bleeding(11). After stopping suppressive chemotherapy, bone marrow healing takes one to three weeks with most agents(12).

Adverse events associated with chemotherapy lead to substantial economic implications(13). A study on patients with ovarian cancer on chemotherapy showed the direct medical costs were highest for neutropenia followed by thrombocytopenia with a mean of $3,268 per episode(14). Similarly, in a retrospective cohort study to estimate the cost of CIT, the total cost incurred related to thrombocytopenia was $1037 per cycle. The surplus cost was as a consequence of increased use of platelet transfusions for prophylaxis(15). Thrombocytopenia can impede surgical interventions and lead to medication delays, dose reduction, or stoppage, which may result in substandard patient outcomes(16).

Thrombocytopenia associated with cancer and its management is understudied in underdeveloped nations, like Kenya. This calls for addressing taking into consideration the high incidence of cancer in these countries. Presently, standardized protocols for the prophylaxis or cure of thrombocytopenia in cancer patients are yet to be established. Main focus has been on the treatment of cancer and not on the adverse effects such as thrombocytopenia. More studies are therefore needed locally to document the risk factors for developing thrombocytopenia, which majorly are related to the cancer type and the treatment given; this study aims at identifying patients with characteristics to cause TCP needing preventive actions and management, which will be of great benefit both clinically and economically.

1.3 Research Questions

i. What is the prevalence of thrombocytopenia in adult cancer patients on cancer treatment at KNH?
ii. What are the risk factors for developing thrombocytopenia among cancer patients?
iii. What is the level of severity of thrombocytopenia in cancer patients?
iv. What are the interventional strategies employed for management of thrombocytopenia in adult cancer patients at KNH?

1.4 Objectives

1.4.1 Main objective

To determine the prevalence of thrombocytopenia, it's risk factors and the management among adult cancer patients at KNH

1.4.2 Specific objectives

i. To estimate the frequency of thrombocytopenia among adult cancer patients undergoing cancer treatment at KNH
ii. To describe the determinants of thrombocytopenia among cancer patients
iii. To recognize the management options employed for thrombocytopenia in the study subjects

1.5 Significance of the study

There has been little attention on the handling of harmful effects of cancer and its treatment. This constitutes a gap in the care of patients, considering the high incidence of the adverse events like thrombocytopenia. Locally, one study estimated its occurrence at 5.6% with radiotherapy as the major risk factor(17).

The findings of this research will be a valuable addition to the body of proof recounting the weight thrombocytopenia has on the management of patients on chemotherapy. In addition, it will highlight the necessity to step in to ensure uninterrupted treatment.

This study provides information regarding patient characteristics which require close observation or prophylactic platelet transfusion. This is of value to patient quality of life as early intervention can reduce length of hospital stay and associated morbidity, mortality and treatment costs.

It gives a valuable insight to guide optimized treatment of cancer patients. The forecasting and deterring of TCP may help clinicians attune the dosages to individual patients and prevent adverse effects(18)**.** In addition, these findings will inform policy makers to increase allocation of resources to better manage cancer patients with adverse events. The recommendations will also aide during formulation and revision of cancer treatment guidelines(19)

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter gives an in-depth description of thrombocytopenia in cancer patients from existing research to gain an understanding of the existing knowledge and debates relevant to this topic. It summarizes information on thrombocytopenia such as its definition, the risk factors and the recommended management. It also identifies the types of cancers and treatment regimens that cause thrombocytopenia.

2.2 Thrombocytes and thrombocytopenia

Platelets are specialized blood cells that regulate haemostasis and thrombosis. They are produced by megakaryocytes which are large bone marrow cells with a lobulated nucleus. They are removed from the bloodstream after 5-7 days in circulation(20). Their role in haemostasis is achieved by the adherence to vascular endothelium to establish a thrombus which eventually prevents significant blood loss. Moreover, they are crucial in inflammation, tissue growth, and the immune response(21).

The mean values of platelet cell count are 266,000 in females and 237,000/microL in males(22). A platelet count from 30 - 50 × 10^9/L seldom causes symptoms, whereas a value of 10 - 30 × 10^9/L platelets leads to bleeding with slightest injury. A count < 10 × 10^9/L may occasion spontaneous bleeding and represents an emergency(5).

Generally, the usual cause of TCP in cancer patients is linked to hindered production of thrombocytes due to a reduction or lack of megakaryocytes, myelosuppression by cytotoxic agents or radiotherapy, or by infiltration of cancer into the bone marrow. However, TCP in malignant diseases may also be due to other causes such as splenic sequestration, immune mediated thrombocytopenia, escalated destruction of platelets as in the case of DIC or microangiopathic anemia(23)

2.2.1 Etiology of thrombocytopenia

The causes of thrombocytopenia are presented is Table 1

Table 1: Causes of thrombocytopenia

Cause	Condition
Lack of or Low megakaryocytes in bone marrow	Aplastic anemia Leukemia Drugs such as cisplatin PNH[1]
Reduced platelet production notwithstanding availability of megakaryocytes	Alcohol-induced thrombocytopenia HIV[2] MDS[3] Vitamins deficiency (B12 or folate)
Platelet sequestration	Liver cirrhosis with congestive splenomegaly Gaucher disease Myelofibrosis with myeloid metaplasia Sarcoidosis
Immunologic destruction	APS[4] CTD[5] Drug-induced thrombocytopenia(for example quinine) HCV[6] Immune thrombocytopenia CLL[7] Neonatal alloimmune thrombocytopenia Post-transfusion purpura Sarcoidosis
Nonimmunologic destruction	Infections (Infectious mononucleosis, CMV, dengue fever) DIC[8] HUS[9] Sepsis ARDS[10] TTP[11]
Dilution	Enormous RBC[12] exchange
Other causes	Pregnancy associated HELLP[13] syndrome

Source: Gauer RL, AFP. 2012;85(6):612-622

[1] Paroxysmal Nocturnal Hemoglobinuria
[2] Human Immunodeficiency Virus
[3] Myelodysplastic syndromes
[4] Antiphospholipid syndrome
[5] Connective tissue diseases
[6] Hepatitis C virus
[7] Chronic lymphocytic leukemia
[8] Disseminated intravascular coagulation
[9] Hemolytic uremic syndrome
[10] Acute respiratory distress syndrome
[11] Thrombotic thrombocytopenic purpura
[12] Red blood cell
[13] Hemolysis, elevated liver enzymes, and low platelets

2.2.2 Pathophysiology of thrombocytopenia

The main processes are drop in bonne marrow platelet generation, destruction in the peripheries, and depletion in DIC, diluted during fluid resuscitation or immense transfusion and sequestering in the spleen due to portal hypertension and/or enlarged spleen(5).

Platelet production depends on normal hematopoietic stem cell function and thrombopoietin production in the liver. A defect leading to megakaryocyte loss in the bone marrow or impairment of liver synthetic function can lead to thrombocytopenia(24). Thrombopoietin regulates the expansion and maturation of megakaryocytes which are hematologic progenitors that give rise to platelets in the bone marrow(25).

The lifespan of platelets is 8-10 days after which they are removed from circulation(26). However, this programmed apoptosis can be accelerated due to antibody mediated clearance. In disseminated intravascular coagulation, platelets are also consumed in thrombi. Massive fluid resuscitation or massive transfusion without proportionate transfusion of platelets is another mechanism of thrombocytopenia(27). Finally, redistribution/hypersplenism also leads to thrombocytopenia. Normally, there is equilibrium between circulating platelets and the platelet mass in the spleen. However, this equilibrium is affected by conditions like cirrhosis that increase splenic size and/or splenic congestion(27).

2.3 Prevalence of thrombocytopenia among cancer patients

Previous research findings estimate that 10 - 38% of solid cancer patients and 40-68% of hematological cancer patients encounter TCP(28). The occurrence of TCP differs with the disease and the type of treatment. It has been indicated that it is frequent in patients with AML 33.4% and ALL 19.1%, aplastic anemia 13.6%, MDS 12.6%, multiple myeloma 9.4%, CLL 6.9%, CML 5.9% and NHL 5.1%. In solid tumors, colorectal cancer, NSCLC, and ovarian cancer recorded high prevalence(29).

In the United States, the prevalence of TCP in all cancer types and all chemotherapy regimens was 21%(30). Likewise, in the Netherlands, TCP was observed in 22% of patients, while South Africa recorded 14.9 %(18). High incidence of thrombocytopenia has been recorded with gemcitabine based regimens at 64.2% and taxane-based chemotherapy regimens at 21.9%. Comparably, higher percentages of TCP were noted in carboplatin monotherapy at 82%, oxaliplatin monotherapy at 50% while with combination therapy, carboplatin based therapies were at 58%, gemcitabine based chemotherapy at 64%, paclitaxel based regimens at 59% and oxaliplatin based chemotherapy regimens at 36%(30). While in Kenya, the prevalence of thrombocytopenia was at 8%(31). Despite being a common toxicity in cancer, there is still limited data on its occurrence(28).

2.4 Empirical review of thrombocytopenia among cancer patients in Kenya

A research done at KNH in the department of oncology found that advanced stage of the disease (stage IV) is linked with increased risk for hemostatic disorders(32). Another similar study among cervical cancer patients in the same facility noted ulcerations, painful urination, TCP and anorexia as the most frequent adverse effects. Most of these patients were on radiotherapy(17). Others found neutropenia as the main hematologic toxicity complicating treatment, while anemia and thrombocytopenia were less experienced. However, severe thrombocytopenia was recorded in some few treatments and patients were given platelet transfusions(33).

2.5 Chemotherapy induced thrombocytopenia (CIT)

This is a platelet count $<150x10^3/\mu L$ in patients on chemotherapy. It usually occurs between 6-10 days following chemotherapy initiation. It is regarded as one of the most regular problems that arise in the course of treatment(34). Chemotherapy induced thrombocytopenia is associated with the type of chemotherapeutic agent. These agents are myelosuppressive and cause thrombocytopenia through various mechanisms. Alkylating agents like busulfan have an effect on pluripotent stem cells (PSCs) while cyclophosphamide and cisplatin influence later megakaryocyte progenitors. Proteosome inhibitors and histone deacetylase (HDAC) inhibitors prevent shedding of platelets by megakaryocytes. Others affect platelet survival by increased platelet destruction

(oxaliplatin, fludarabine, gemcitabine, mitomycin-C), increased apoptosis (venetoclax, cisplatin) and via reduced kinase activity (desatinib, imatinib, sunitinib) (35).

2.6 Other Causes of thrombocytopenia among cancer patients on chemotherapy

Additional causes of significant thrombocytopenia amongst cancer patients include immune thrombocytopenia, coagulopathy, infection, drug reaction, post-transfusion purpura, and thrombotic microangiopathy(36).

Immune thrombocytopenic purpura (ITP) is a disorder that is mediated by autoantibodies that are developed against proteins of the platelet membrane, which results in sequestration of these coated cells and removal by macrophages. It gets down to reduced platelet count. Peripheral blood smear in this condition indicates low platelets with typical appearing neutrophils and erythrocytes (37). Immune thrombocytopenia occurs mostly in CLL, HL and NHL with prevalence of 1-5%, 0.2-1% and 0.76% respectively.

Various illnesses such as cancer with a systemic impact may cause activation of coagulation manifesting as DIC. Disseminated intravascular coagulation then causes depletion of thrombocytes(38). Cases of TCP due to DIC are estimated at an incidence of 1.6–6.8% in cancer. The risk factors include old age and adenocarcinoma. Bleeding or thrombotic complications may be the first signs of DIC(39).

Common viruses that cause thrombocytopenia include HBV, HCV, HIV, EBV, CMV, mumps, rubella and parvovirus B19. Travel associated infections such as dengue fever; malaria and typhoid fever also cause thrombocytopenia. The mechanisms of thrombocytopenia by these infections are either by suppressing the bone marrow or destruction of platelets peripherally(5).

Drug induced thrombocytopenia (DITP) is always thought of when there is a severe fall in platelet count. In the setting of DITP, majority of patients experience moderate to severe TCP reaching a count of 20×10^3 /μL platelets. Thrombocytopenia generally resolves quickly after the offending medication withdrawn. It usually manifests in less

than seven days of use and settles within seven to fourteen days after stopping(40). A 2013 systematic review on drug induced thrombocytopenia found the following drugs to be directly involved in DITP reactions: quinine, ceftriaxone, GP IIb/IIIa inhibitors (eftifibatide), quinidine, vancomycin, trimethoprim-sulfamethoxazole, suramin, rifampin, penicillin, mirtazapine, carbamazepine, heparin, ibuprofen and oxaliplatin(41).

Post Transfusion Purpura (PTP) is an infrequent but significant complication marked by severe TCP emerging within 2 weeks of transfusion. It comes about when a recipient with an antiplatelet antibody receives thrombocytes expressing the corresponding antigen(42). It is mostly encountered in a multiparous woman or in a recipient who has developed anti-HPA-1a antibodies from earlier transfusion. Generally, it settles in 2 weeks without intervention but quick restoration takes place following high-dose of IVIG or with plasmapheresis treatment(42).

2.7 Risk factors for thrombocytopenia among cancer patients

Thrombocytopenia is diagnosed when the number of platelets in blood is low. In cancer patients, the commonest risk factors are chemotherapeutic agents and radiotherapy by bone marrow suppression (BMS). The agents mostly implicated include topotecan, vinorelbine, paclitaxel, anthracycline, carboplatin, methotrexate and gemcitabine which pose a higher risk, while bleomycin, asparaginase, pemetrexed, vincristine and cisplatin have a lower risk(43). Bone marrow cancer involvement also has a high risk of thrombocytopenia being led by hematological malignancies such as leukemias and lymphomas(28).

Similarly, co-morbidities which include liver diseases, hypersplenism, infection, rheumatic diseases and hypothyroidism are also risks for TCP. It is also a common finding in HELLP syndrome during pregnancy. Finally, studies have indicated that aging, nutritional deficiencies (low levels of vitamin B12 or folate) and alcohol use increase the risk of thrombocytopenia(43).

Recent studies concluded that an increase of age up to 10 years corresponded to a decrease in platelet counts of 9×10^9/L. These findings indicated that there is a 35% decrease of platelets counts in older men and 25% in older women in comparison to infancy(44). Moreover, platelet counts differ slightly, between men and women, being higher in women in all age groups by approximately 10%(44).

It has been hypothesized that higher BMI leads to changes in platelet characteristics which contributes to an increased number of immature platelets, which is associated with greater whole blood platelet aggregation(45). A study on the effect of cigarette smoking on thrombocytopoiesis found that the mean platelets count increased significantly with smokers compared to non-smokers. It further concluded that platelets count is reduced in individuals with alcohol use disorder(46)

2.8 Management of thrombocytopenia in cancer patients

Cancer patients have different degrees and duration of thrombocytopenia which depend on the type of cancer, chemotherapy agents used, cancer involvement of the bone marrow and other comorbidities.

Conventional protocols for the management of TCP in cancer patients is yet to be put in place(47). Generally, with counts < 100×10^3/µL of platelets, chemotherapy dose is typically modified, delayed, or substituted to avoid further exacerbations of thrombocytopenia which leads to spontaneous bleeding tendencies. However, platelet transfusion is administered when it reaches values <10×10^3/µL, or when there is active bleeding and also in situations where sustaining the drug dose is dire for survival.

A study in the United Kingdom documented that more than 10% of patients developed thrombocytopenia with platelet count < 75 x 10^9/L. This led to dose delay in 35% of the cases, dose reduction in 36% of cases, hospitalization due to active bleeding in 32% of cases and 7% of cases were discontinued with therapy(48).

The potential negative consequences with chemotherapy dose modification are the decrease in relative dose intensity (RDI), reduced treatment efficacy and risk of high residual rates of bleeding even with platelet transfusion. With these challenges still unmet, there are some ongoing studies on antifibrinolytics and thrombopoietin receptor agonists, which promise to help maintain chemotherapy dose intensity(35).

Thrombopoietin receptor agonists help boost platelets and have been accepted for the management of some TCP conditions. Orphan drug designation was recently awarded to avatrombopag by USA (FDA) for TCP treatment, while phase III trials are in progress. During phase II trial for solid tumors, 85% of romiplastin treated patients for CIT resulted in platelet restoration which allowed chemotherapy to continue as anticipated(49).

In China, recombinant human thrombopoietin (rhTPO) and recombinant human interleukin-11 (rhIL-11) have been approved for management of CIT. These medications are started when platelets count is between $10x10^9$ and $75x10^9$ cells per liter. Recombinant human thrombopoietin (rhTPO) is prepared from Chinese hamster and it has similar effects as endogenous thrombopoietin. It is better than rhIL-11 at raising platelet count and reducing the span of TCP. Use rhIL-11 is limited because of the narrow therapeutic index and serious side effects which include edema and arrhythmia(50).

2.9 Literature gap

After going through literature on thrombocytopenia in cancer patients, standardized approaches to CIT are still under development and yet to established. Poor intervention of TCP in these patients causes increased morbidity and mortality. Many studies are ongoing on the new regimens that give a promise of better approach to CIT. Early identification of the risk factors which could lead to thrombocytopenia is valuable in saving lives and improving standard of living. Findings in this current work could be timely for these identified gaps.

2.10 Conceptual Framework

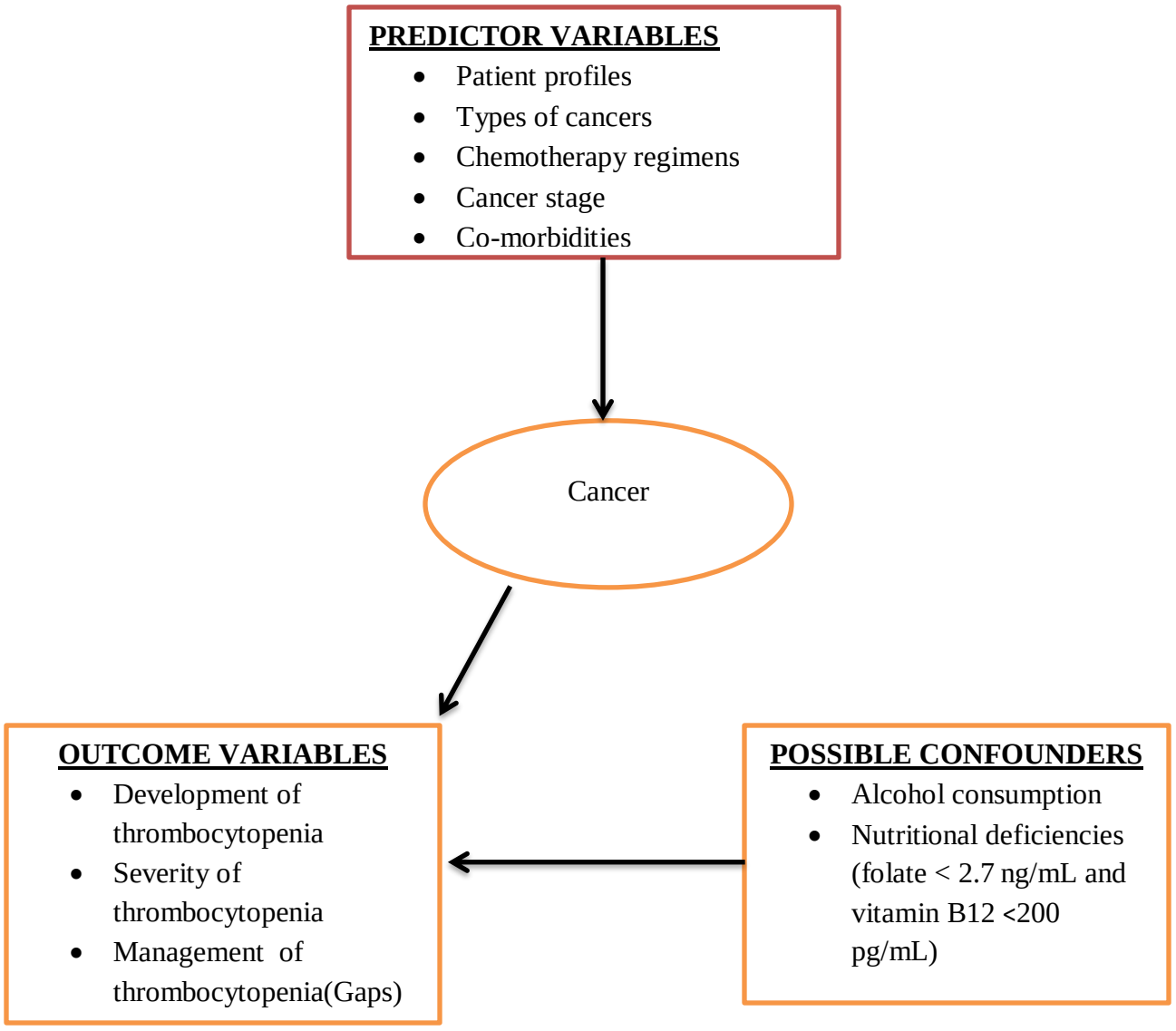

Figure 1: Conceptual Framework for prevalence of thrombocytopenia

The conceptual framework shows how the variables interact with each other. Adult cancer patients who were initiated on chemotherapy between January 2019 and June 2022 make up this study. Prevalence of thrombocytopenia in the study population, risk

factors and its management are the objectives of the study. A higher prevalence of thrombocytopenia is associated with gaps in treatment. The risk factors for thrombocytopenia include the patient profiles like age, type of chemotherapy regimens and cancer type. Alcohol consumption and malnutrition are possible confounders that need to be controlled. A cross-sectional study design was ideal to meet these objectives.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This is a synopsis on how the objectives in this study were realized and how the questions were answered. It details the study design, location of the study and the target population. It also states the eligibility criteria and sample. It further explains the research instruments, ethical considerations, data collection techniques and analysis.

3.2 Study design

Cross-sectional study design was used to assess the prevalence, risk factors and interventional strategies for thrombocytopenia in adult cancer patients who were initiated on chemotherapy between January 2019 and June 2022. This study design was ideal in attaining the objectives of the study. It is relatively easy and economical to conduct because it does not require follow-up. It is also quick to conduct since the exposure and outcome status are determined at the same time which was necessary for the short period of data collection in this study. Finally, it was the ideal study design as it can be both descriptive and analytical which was essential in this study.

3.3 Study setting

It was carried out at Kenyatta National Hospital (KNH)-Cancer Treatment Center (CTC). Kenyatta National Hospital is located in Nairobi and is the most extensive referral facility in Kenya, being of service to a population of over 4 million with a 2000 bed capacity. The Hospital receives cancer patients who travel from all corners of the country and the region to access treatment. It is one of the few facilities in Kenya that offers advanced comprehensive cancer treatment to patients. The site was ideal because it allowed the achievement of the required sample size for the study.

3.4 Target population and study population

The target population consisted of all adult cancer patients on cancer treatment at KNH-CTC, whereas the study population comprised of all adult cancer patients initiated on cancer treatment between January 2019 and June 2022 at KNH-CTC and met the eligibility criteria.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

1. Adult cancer patients above 18 years
2. Patients undergoing cancer treatment at KNH-CTC between January 2019 and June 2022

3.5.2 Exclusion criteria

1. Patients with incomplete records

3.6 Sample size estimation

The prevalence of thrombocytopenia among CML Patients on Imatinib in Kenya was estimated to be 8%(31). To determine the sample size in this study, the Cochran formula was employed (Equation 1). It takes into consideration the margin error and also the level of acceptable risk. This formula was appropriate because the study was a survey aimed at computing the prevalence(51).

Equation 1: Cochran formula

$$n = \frac{pqz^2}{e^2}$$

n: desired sample size

p: prevalence of thrombocytopenia from literature

q: the desired level of precision (1-p)

z: the standard deviation for 95% confidence interval which is 1.96

e: safety margin, 0.05%

Therefore:

$$n = \frac{0.08x\ (1-0.08)\ x1.96^2}{0.05^2}$$

n= 113

To cater for missing records, the sample size was adjusted by 20%

$$n = \frac{120}{100} \times 113 = 136 \text{ files}$$

Therefore, 136 participants (patient files) were studied

3.7 Sampling and retrieval of participant files

After receiving permission to conduct the study from ERC, the researcher wrote to the KNH Research office and head of oncology department for permission to conduct the study. The records department was requested to provide a list of all adult cancer patients seen between January 2019 and June 2022. These files were checked if the participants met the eligibility criteria with the aid of the eligibility check list in Appendix A. The desired sample size was then drawn by systematic sampling, where all the files were assigned a number, then decision was made on the sampling interval by dividing the population size by the desired sample size. A starting point was chosen by selecting a random number. For instance, if the starting point is 10 and the sampling interval is 100, then the first member of the sample would be 110.

3.8 Research instruments

A data collection tool (appendix B) was used to collect relevant information necessary to meet the objectives of this study. Data collected included participants' biodata, type of cancer and treatment modalities, co-morbidities which include liver disease, deep vein thrombosis, kidney disease, hypersplenism, sepsis and HELLP syndrome(52). Information on the platelet counts and interventions for thrombocytopenia was also retrieved.

3.9 Pre-test

A pre-test was carried out on approximately 10% of the study population. This informed whether the tool could collect data that can answer the research questions and meet the objectives of the study. After the exercise, necessary modifications were made and the revised tool was submitted to KNH/UoN-ERC for approval.

3.10 Quality assurance

A well designed tool approved by the KNH/UON-ERC was used for data collection. Data were verified and cleaned to ensure that any errors are avoided during data analysis. Further, regular meetings were held with the supervisors and progress reports submitted to ensure that any deviation from protocol is captured and addressed.

Internal validity was ensured by use of relevant study design, proper conduct of the study with pre-tested data collection instrument and correct analysis of the results.

3.11 Data collection

This was done in duration of 3 months from May to August 2023. Data were collected by both the researcher and one research assistant recruited and well trained by the researcher on the methodology of the study and the data collection tool. He was in his final year at the University of Nairobi doing Bachelor of Pharmacy. The exercise was conducted by abstracting relevant information from patient files with the aid of the data collection instrument (Appendix B). The information collected included participant's biodata, cancer type, platelets count, cancer treatment, comorbidities and interventions for thrombocytopenia. Thrombocytopenia was defined as platelet counts < 150 $x10^3$ cells per µL, with severity as: mild < 100 – 150 $x10^3$/µL, moderate from 50 – 99 x 10^3/µL and severe <50 x 10^3/µL.

3.12 Data management

Data were entered into Microsoft Excel sheet within 24 hours of data collection and then coded. The database was password protected and only accessible to the principal investigator (PI). A backup system was by the use of an external drive that was updated regularly and kept under lock and key. All hard copies containing the raw data were put in a lockable cabinet with limited access only to the principal investigator. Data was then cleaned and exported into STATA statistical analysis software version 13 for analysis.

3.13 Study variables

Independent variables

These included participant's sociodemographic characteristics such as age, gender, smoking and alcohol consumption. In addition, the clinical characteristics and cancer treatment modalities were also in this group.

Dependent variables

The dependent variables were the presence and severity of thrombocytopenia and the interventional strategies employed for thrombocytopenia.

3.14 Data analysis

Data was analyzed using STATA statistical software version 13. Descriptive data analysis was carried out, with categorical variables summarized by percentages and frequencies. Continuous data was summarized by median and interquartile range. Thereafter, inferential data analysis to determine association between the variables was conducted. Binary logistic regression was used to determine the relationship between thrombocytopenia and explanatory variables. Multivariate logistic regression was then conducted for all the variables that were associated with the outcome variable with a p-value of less than 0.05 during the bivariate analysis. A p-value$\leq$0.05 was used as statistical significant and together with adjusted odds ratio with 95% confidence interval were used to indicate the strength of association.

Prevalence = the proportion of the total population that has the outcome at a specific point in time

$$\textbf{CI} = \frac{\textbf{Number of cases}}{\textbf{Total population of interest}}$$

3.15 Ethical considerations

Application for approval to conduct the study was made to KNH/UoN-ERC which was granted, reference number p817/10/2022 (Appendix C). An additional approval was sought from the KNH Research and Programs department and oncology department, study registration number CTC/177/2023 (Appendix D).

To ensure confidentiality, unique codes were used to identify participants instead of real names. Access to data was limited to the principal investigator as hard copies were placed under lock and key whereas electronic data was password protected.

This was a low-risk study since it was an observational study where there was no direct contact with patients. This study will be of benefit to patients on chemotherapy, prescribers and also policy makers in improving management of cancer patients.

CHAPTER 4: RESULTS

4.1 **Socio demographic traits of sampled cancer patients**

Out of the 137 patients, more than half (93, 67.9%) were female while (44, 32.1%) were male. Majority (51, 37.2%) were above 60 years. The median age was 52 (IQR=25, 79) years. Majority (49, 45%) had attained secondary level of education, were self-employed (56, 46.7%) and married (107, 79%). Most of the respondents were neither smoking (112, 88.9%) nor taking alcohol (110, 87.3%), as shown in Table 2.

Table 2: Socio-demographic characteristics of cancer patients at KNH

		Frequency (n=137)	**Percentage**
Gender	Female	93	67.9
	Male	44	32.1
Age	Below 30	11	8.0
	31-40 years	24	17.5
	41-50 years	22	16.1
	51-60 years	29	21.2
	Above 60 years	51	37.2
	Median	**52(IQR=25, 79)**	
Level of education	Primary	36	33.0
	Secondary	49	45.0
	Tertiary	19	17.4
	None	5	4.6
Occupation	Unemployed	28	23.3
	Self-Employed	56	46.7
	Employed	36	30.0
Marital status	Single	15	11.1
	Married	107	79.3
	Widowed	9	6.7
	Divorced	1	0.7
	Separated	3	2.2
Smoking	Yes	14	11.1
	No	112	88.9
Alcohol	Yes	16	12.7
	No	110	87.3

4.2 Counties of origin of study participants

The highest frequency came from Nairobi county (39, 28.5%) followed by Kiambu (19, 13.9%) and Murang'a (16, 11.7%).

Table 3: Counties of origin of cancer patients at KNH

County	Frequency	Percentage
Nairobi	39	28.5
Kiambu	19	13.9
Murang'a	16	11.7
Nyeri	9	6.6
Meru	8	5.8
Kisii	6	4.4
Makueni	4	2.9
Migori	3	2.2
Siaya	3	2.2
Kisumu	3	2.2
Embu	3	2.2
Bungoma	2	1.5
Kajiado	2	1.5
Kericho	2	1.5
Laikipia	2	1.5
Nakuru	2	1.5
Nyandarua	2	1.5
Bomet	1	0.7
Busia	1	0.7
Garissa	1	0.7
Homabay	1	0.7
Kirinyaga	1	0.7
Kwale	1	0.7
Marsabit	1	0.7
Mombasa	1	0.7
Nyamira	1	0.7
Tharaka-Nithi	1	0.7
Machakos	1	0.7
Trans-Nzoia	1	0.7
n	**137**	**100**

4.3 Clinical characteristics of participants

4.3.1 Cancer type among participants

Most (108, 79%) of the patients had solid cancers while the rest 29(21%) had hematological cancers. The prevalence of each cancer type is as shown in figure 2.

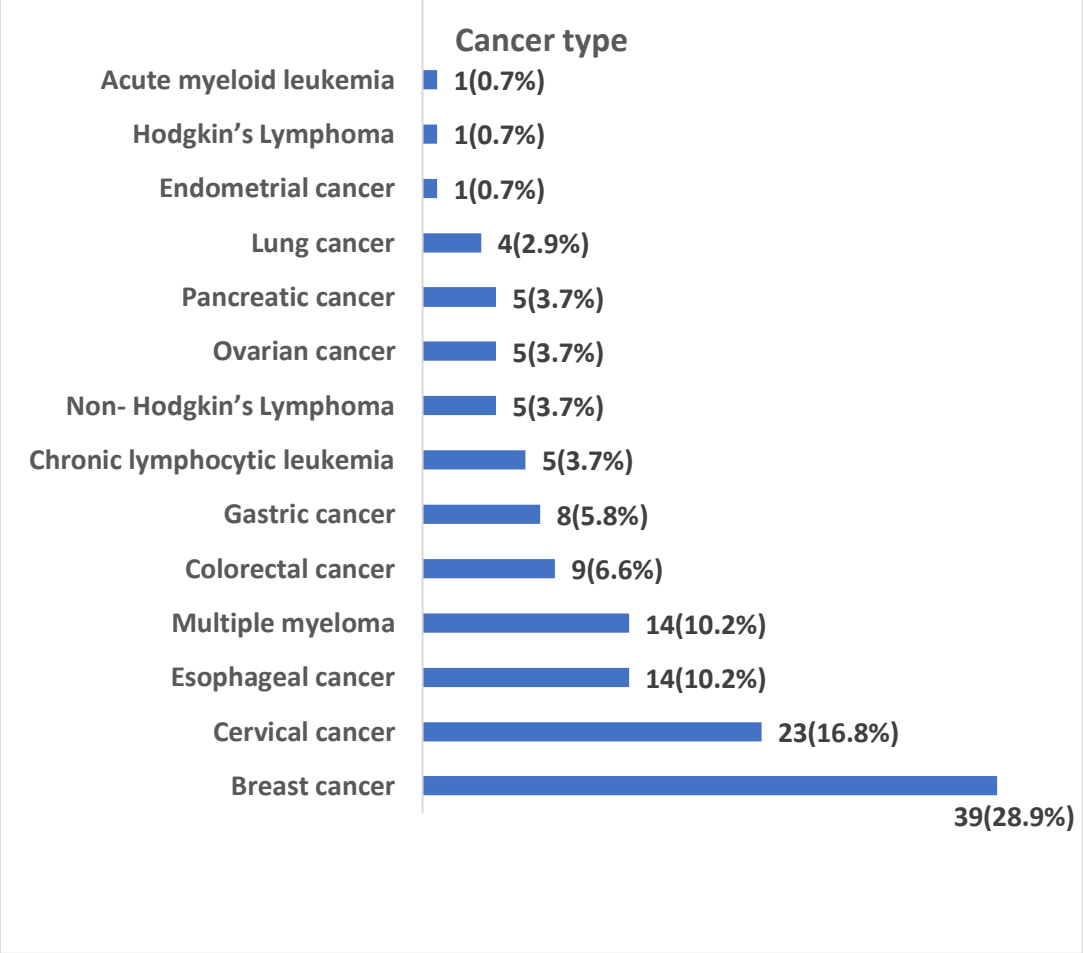

Figure 2: The prevalence of each cancer type in cancer patients at KNH

Breast cancer was the most common type of cancer among the patients (39, 28.9%), followed by cervical cancer (23, 16.8%), esophageal cancer and multiple myeloma which had the same frequencies (14, 10.2%). The least prevalent cancer types were acute myeloid leukemia, Hodgkin's lymphoma, endometrial cancer and chronic myelogenous leukemia.

4.3.2 Cancer stage among study participants

Most of the participants were in cancer stage IV 48(35.6%), followed closely by those that were not staged 45(33.3%). Stages III, II and I were (22, 16.3%), (8, 5.9) and (12, 8.9%) respectively

4.3.3 Comorbidities among study participants

Out of the 137 participants, (22, 16.1%) had liver disease, (16, 11.8%) had kidney failure, (4, 2.9%) had deep vein thrombosis, (2, 1.5%) had sepsis and thyroid disorders and few (1, 0.7%) had HELLP syndrome.

Table 4: Concomitant conditions among cancer patients at KNH

Concomitant conditions	Frequency	Percentage
Liver disease	22	16.1
Kidney failure	16	11.8
Deep vein thrombosis	4	2.9
Sepsis	2	1.5
Thyroid disorders	2	1.5
HELLP syndrome	1	0.7

4.4 Anticancer agents used by study participants

Majority (45, 32.9%) of the study participants were not in any chemotherapy regimens. Doxorubicin and cyclophosphamide was the mostly used chemotherapeutic combination (13, 9.5%) followed by cisplatin and paclitaxel (12, 8.8%). Doxorubicin, cyclophosphamide and paclitaxel combination was (7, 5.1%), same as combination between folinic acid, fluorouracil and oxaliplatin, while carboplatin and paclitaxel was (6, 4.4%). The rest of the regiments were least used by the patients as shown in table 5.

Table 5: Chemotherapeutic agents used by cancer patients at KNH

Chemotherapy agents	Frequency	Percentage
Doxorubicin and cyclophosphamide (AC)	13	9.5
Cisplatin and Paclitaxel	12	8.7
Doxorubicin, Cyclophosphamide and Paclitaxel (ACT)	7	5.2
Fluorouracil, Folinic Acid and Oxaliplatin (FOLFOX)	7	5.2
Carboplatin and Paclitaxel	6	4.4
Capecitabine and Oxaliplatin (CAPOX)	5	3.7
Cyclophosphamide, Vincristine, Doxorubicin and Prednisolone (CHOP)	4	2.9
AC-Trastuzumab	4	2.9
Chlorambucil, Prednisolone	3	2.2
AC-Trastuzumab and Paclitaxel	2	1.5
Bortezomib, Cyclophosphamide and Dexamethasone	2	1.5
Cisplatin	2	1.5
Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel (FLOT)	2	1.5
Fluorouracil, Folinic Acid, Irinotecan and Oxaliplatin (FOLFIRINOX)	2	1.5
Melphalan and Prednisone (MP)	2	1.5
Rituximab, Cyclophosphamide, Vincristine and Prednisone (R-CVP)	2	1.5
Lenalidomide, Bortezomib and Dexamethasone) RVD	2	1.5
Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD)	1	0.7
AC-Tamoxifen	1	0.7
Azacitidine	1	0.7
Bendamustine and Mephalan	1	0.7
Bleomycin, Etoposide and Cisplatin (BEP)	1	0.7
Capecitabine	1	0.7
Cisplatin and Etoposide	1	0.7
Cyclophosphamide, Prednisolone and Thalidomide	1	0.7
Dexamethasone and Thalidomide	1	0.7
Fluorouracil, Folinic Acid and Irinotecan (FOLFIRI)	1	0.7
Gemcitabine and cisplatin (GEMCIS)	1	0.7
Imatinib	1	0.7
Melphalan, Prednisone and Thalidomide (MPT)	1	0.7
Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP)	1	0.7
Paclitaxel, Doxorubicin and cisplatin (TAP)	1	0.7
None	45	32.8
Total	137	100%

4.5 Prevalence of thrombocytopenia among study participants

Among the 137 study participants, 43(31.4%) had thrombocytopenia. Severity of thrombocytopenia was defined as mild ((100,000-150,000/µL platelets), moderate (50,000-99,000/µL platelets) and severe (<50,000/µL platelets). For the cancer patients with thrombocytopenia, 20(47.6%) had mild thrombocytopenia, 7(16.7%) were with moderate thrombocytopenia and 15(35.7%) had severe thrombocytopenia.

Among the 43 cases of thrombocytopenia, the condition was more prevalent in women at 24(17.6%) compared to men 24(14.0%) and this was statistically significant (p=0.032). It was also noted that thrombocytopenia was more prevalent for the ages above 60 at 19(14.0%) followed by those below 30 years, however, this was not significant (p=0.501). Thrombocytopenia was (32, 23.7%) prevalent in married participants, while among the single, widowed, divorced and separated it was (6, 4.5%), (3, 2.2%), (0, 0%) and (1, 0.7%) respectively. Marital status was not statistically significant (p=0.878). The condition had a prevalence of (7, 5.1%) in smokers and (6, 4.5%) in alcohol consumers. Smoking and alcohol consumption were not statistically significant, (p=0.091) and (p=0.389) respectively, as indicated in table 6.

Table 6: Comparison of the socio demographic traits of cancer patients with and without thrombocytopenia at KNH (N=137)

N=137	Demographic characteristics	Number with thrombocytopenia N (%)	Number without thrombocytopenia N (%)	P value
Gender	Female	24(17.6%)	69(50.7%)	
	Male	19(14.0%)	24(17.6%)	**0.032**
Age	Below 30	4(2.9%)	7(5.1%)	
	30-40 yrs	4(2.9%)	20(14.7%)	
	40-50 yrs	7(5.1%)	15(11.0%)	
	50-60 yrs	9(6.7%)	19(14.0%)	
	Above 60 yrs	19(14.0%)	32(23.5%)	0.501
Marital status	Single	6(4.5%)	9(6.7%)	
	Married	32(23.7%)	75(56.0%)	
	Widowed	3(2.2%)	6(4.5%)	
	Divorced	0(0.0)	1(0.7%)	
	Separated	1(0.7%)	2(1.5%)	0.878
Smoking	Yes	7(5.1%)	7(5.1%)	
	No	31(22.8%)	80(67%)	0.091
Alcohol	Yes	6(4.5%)	9(6.7%)	
	No	32(23.5%)	78(65.3%)	0.389

Concerning the clinical characteristics of study participants, thrombocytopenia was most prevalent in participants with multiple myeloma (12, 8.8%), followed by chronic lymphocytic leukemia (6, 4.4%). It was most prevalent in participants with stage IV disease (13, 9.6%) followed closely in those on stage III (10, 7.4%). Kidney failure was associated with the highest prevalence of thrombocytopenia (10, 21.3%) followed by liver disease (7, 14.9%). Thrombocytopenia was (19, 14.0%) prevalent in participants who were on radiotherapy. There was statistically significant relationship between cancer type and thrombocytopenia ($p < 0.0001$) as shown below in table 7.

Table 7: Prevalence of TCP in clinical features of cancer patients at KNH

Clinical features		With thrombocytopenia n (%)	Without thrombocytopenia n (%)	p value
Cancer type	Multiple myeloma	12(8.8%)	2(1.5%)	
	Chronic lymphocytic leukemia	6(4.4%)	1(0.7%)	
	Breast cancer	5(3.7%)	34(25.0%)	
	Cervical cancer	5(3.7%)	18(13.2%)	
	Non- Hodgkin's Lymphoma	3(2.2%)	2(1.5%)	
	Lung cancer	2(1.5%)	2(1.5%)	
	Colorectal cancer	2(1.5%)	7(5.1%)	
	Esophageal cancer	2(1.5%)	11(8.0%)	
	Gastric cancer	1(0.7%)	7(5.1%)	
	Ovarian cancer	1(0.7%)	4(1.1%)	
	Pancreatic cancer	1(0.7%)	4(1.1%)	
	Endometrial cancer	0(0.0%)	1(0.7%)	
	Hodgkin's Lymphoma	1(0.7%)	0(0.0%)	
	Acute myeloid leukemia	1(0.7%)	0(0.0%)	
	Chronic myelogenous leukemia	1(0.7%)	0(0.0%)	**0.000**
Cancer stage	Stage I	0(0.0%)	12(8.9%)	
	Stage II	2(1.5%)	6(4.4%)	
	Stage III	10(7.4%)	12(8.9%)	
	Stage IV	13(9.6%)	35(25.9%)	
	Not staged	17(12.6%)	28(20.7%)	0.062
Concomitant conditions	Deep vein thrombosis	2(4.3%)	2(4.3%)	
	HELLP syndrome	0(0.0%)	1(2.1%)	
	Kidney failure	10(21.3%)	6(12.8%)	
	Liver disease	7(14.9%)	15(31.9%)	
	Sepsis	1(2.1%)	1(2.1%)	
	Thyroid disorders	2(4.3%)	0(0.0%)	0.24
Radiotherapy	Yes	19(14.0%)	38(27.9%)	
	No	24(17.1%)	55(40.4%)	0.853

With regard to chemotherapy regimens, thrombocytopenia was most prevalent among patients on cyclophosphamide based regimens (10, 10.9%). This was statistically significant p=0.002. It was then followed by carboplatin based combination with a prevalence of thrombocytopenia at (6, 6.5%) and statistically significant (p value 0.012). The condition had a prevalence of (5, 5.4%) in cisplatin based combination and it was

statistically significant (p=0.007). In oxaliplatin based combination, it was (4, 4.3%) prevalent and was also statistically significant p value 0.002, while thalidomide-based combination, chlorambucil based combination and melphalan based combination, all had the same prevalence of thrombocytopenia (3, 3.3%) and was not statistically significant (p=0.688, p=0.641, p=0.700 respectively). The other combinations which included ABVD, FOLFIRI and imatinib had a prevalence of thrombocytopenia of (3, 3.3%) and this was a statistically significant relationship, with a p value of 0.038 as shown in table 8.

Table 8: Prevalence of TCP by chemotherapeutic regimen in cancer patients at KNH

Chemotherapy regimens	Frequency (N=35)	%	p-value
Cyclophosphamide based	**10**	**27.3**	**0.002**
AC	1	2.7	
AC-TRASTUZUMAB	1	2.7	
AC-trastuzumab, paclitaxel	1	2.7	
ACT	1	2.7	
Bortezomib, cyclophosphamide, dexamethasone	1	2.7	
Cyclophosphamide, prednisolone, thalidomide	1	2.7	
CHOP	2	5.4	
R-CHOP	1	2.7	
R-CVP	1	2.7	
Carboplatin based	**6**	**16.2**	**0.012**
Carboplatin, paclitaxel	6	20.7	
Oxaliplatin based	**4**	**10.8**	**0.002**
CAPOX	2	5.4	
FOLFIRINOX	1	2.7	
FOLFOX	1	2.7	
Cisplatin based	**5**	**13.5**	**0.007**
Cisplatin Paclitaxel	3	8.1	
BEP	1	2.7	
Cisplatin etoposide	1	2.7	
Mephalan based	**3**	**8.1**	0.700
MP	2	5.4	
Bendamustine, mephalan	1	2.7	
Chlorambucil based	**3**	**8.1**	0.641
Chlorambucil, prednisolone	3	8.1	
Thalidomide based	**3**	**8.1**	0.688
Dexamethasone, thalidomide	1	2.7	
RVD	2	5.4	
Others	**3**	**8.1**	**0.038**

Others include: ABVD, FOLFIRI and imatinib.

Concerning use of other medications, ceftriaxone was the only medication used by 23 participants within 7 days of the recorded lab values. None of the participants had thrombocytopenia.

4.6 Risk factors for thrombocytopenia among cancer patients at KNH

4.6.1 Bivariate analysis

Findings in table 9 outline the association between the socio-demographic traits of participants and thrombocytopenia. Females had 2 times the odds of having thrombocytopenia as compared to the male participants (OR=2.276, 95% CI, 1.064, 4.868 P=**0.034**), and this was statistically significant. Participants with secondary level education had 3 times the odds of having thrombocytopenia compared to the other levels, this was also statistically significant (OR=3.091, 95% CI, 1.211, 7.891 **p=0.018**). In addition, participants who were formally employed had 0.2 times the odds of having thrombocytopenia compared to those with other employment status, which was statistically significant (OR=0.272, 95% CI, 0.084, 0.875 **p=0.029**).

Table 9: Association between socio demographic traits of cancer patients and thrombocytopenia at KNH

				CI 95%	
		Crude OR	**Lower**	**Upper**	**P-Value**
Age	Below 30 years	**Ref**			
	30-40 years	2.857	0.559	14.603	0.207
	40-50 years	1.224	0.267	5.605	0.794
	50-60 years	1.206	0.28	5.206	0.801
	Above 60 years	0.962	0.249	3.725	0.956
Gender	Male	REF			
	Female	2.276	1.064	4.868	**0.034**
Marital status	Single	**Ref**			
	Married	1.61	0.529	4.916	0.840
	Widowed	1.33	0.237	7.51	0.330
	Divorced	1			
	Separated	1.33	0.098	8.192	0.442
Level of education	Primary	**Ref**			
	Secondary	3.091	1.211	7.891	**0.018**
	Tertiary	1.938	0.603	6.232	0.267
	None	3.579	0.274	35.232	0.274
Occupation	Student	**Ref**			
	Self-Employed	0.423	0.139	1.289	0.130
	Employed	0.272	0.084	0.875	**0.029**
Smoking	No	**Ref**			
	Yes	0.388	0.126	1.196	0.099
Alcohol	No	**Ref**			
	Yes	0.615	0.202	1.871	0.392

Table 10 shows the association between thrombocytopenia and the clinical characteristics of study participants. The findings indicate that participants with hematological malignancies have 22 times the odds of having thrombocytopenia compared to those with solid malignancies, this was statistically significant (OR=22.23, 95% CI 7.523, 65.7 **P<0.001**.

Table 10: Association between the clinical factors of cancer patients and thrombocytopenia at KNH

			CI 95%		
		Crude OR	**Lower**	**Upper**	**P-Value**
Cancer stage	Stage I	**Ref.**			
	Stage II	1.821	0.329	10.071	0.492
	Stage III	0.729	0.259	2.047	0.548
	Stage IV	1.634	0.680	3.927	0.272
	Not staged	1			
Cancer type	Solid	**Ref.**			
	Hematological	22.23	7.523	65.7	**0.000**
Concomitant conditions	Deep vein thrombosis	**Ref.**			
	HELLP syndrome	1			
	Kidney failure	0.6	0.066	5.447	0.650
	Liver disease	2.142	0.248	18.489	0.650
	Sepsis	1	0.034	29.81	1.000
	Thyroid disorders	1			

Table 11 demonstrates the association between thrombocytopenia and different categories of chemotherapeutic agents used by the study participants. The findings show that there was a significant association between Thrombocytopenia and the following regimens: cyclophosphamide based regimens (p 0.002), carboplatin based regimens (p 0.012), oxaliplatin based regimens (p 0.002), and cisplatin based regimens (p 0.007). The other regimens which include ABVD, FOLFIRI and imatinib also showed significant relationship with thrombocytopenia (p 0.038). There was however no significant association with mephalan based (p=0.700) chlorambucil based (p=0.641) and thalidomide based regimens (0.688).

Table 11: Association between chemotherapy regimens and thrombocytopenia in cancer patients at KNH

Chemotherapy regimens	CI 95%		P value
	Lower	Upper	
Cyclophosphamide based			**0.002**
Carboplatin based	0.007	0.577	**0.012**
Oxaliplatin based	0.306	9.080	**0.002**
Cisplatin based	0.236	3.630	**0.007**
Mephalan based	0.011	1.329	0.700
Chlorambucil based			0.641
Thalidomide based			0.688
Others	0.124	3.072	0.038

4.6.2 Multivariate logistic regression

Table 12 gives results of multivariate analysis of the variables that showed significant association with thrombocytopenia in the bivariate analysis. This is done to control of confounders. The results indicate that hematological malignancies and carboplatin based regimens have a statistically significant association with the outcome. Participants with hematological malignancies have 0.02 times the odds of having thrombocytopenia compared to those with solid malignancies ($p<0.001$). The findings further demonstrates that participants on carboplatin based regimens have 0.06 times the odds of having the condition as compared to the participants on the other regimens ($p=0.015$).

Table 12: Multivariate analysis on statistically significant variables in cancer patients at KNH

			CI 95%		
		Adjusted OR	**Lower**	**Upper**	**P-Value**
Gender	Male	**Ref.**			
	Female	0.530	0.145	1.941	0.338
Occupation	Student	Ref.			
	Self-Employed	0.466	0.097	2.244	0.341
	Employed	0.211	0.037	1.191	0.078
Level of Education	Primary	**Ref.**			
	Secondary	2.383	0.686	8.277	0.172
	Tertiary	3.142	0.667	14.805	0.148
	None	0.433	0.029	6.470	0.544
Cancer type	Solid	**Ref.**			
	Hematological	0.025	0.005	0.129	**≤0.001**
Chemotherapy regimens	Cyclophosphamide based	**Ref.**			
	Carboplatin based	0.062	0.007	0.577	**0.015**
	Oxaliplatin based	1.667	0.306	9.080	0.555
	Cisplatin based	0.926	0.236	3.630	0.912
	Mephalan based	0.123	0.011	1.329	0.085
	Chlorambucil based	1.000			
	Thalidomide based	1.000			
	Others	0.617	0.124	3.072	0.556

4.7 Interventions for thrombocytopenia among study participants

In comparison with the types of interventions given, 19(45.2%) of the cancer patients who had mild thrombocytopenia and 2(4.8%) who had severe thrombocytopenia received no interventions. The patients who received platelets transfusion were 12(28.6%) with severe, 7(16.7%) moderate and only 1(2.4%) with mild thrombocytopenia. Only 1(2.4%)

patient with severe thrombocytopenia had chemotherapy dose delay as shown in table 13 below.

Table 13: Severity of thrombocytopenia and interventions in cancer patients at KNH

		Severity of thrombocytopenia		
	N=42	**Mild n (%)**	**Moderate n (%)**	**Severe n(%)**
Interventions given	No intervention	19(45.2%)	0	2(4.8%)
	Platelet's transfusion	1(2.4%)	7(16.7%)	12(28.6%)
	Chemotherapy dose delay	0	0	1(2.3%)
	Total	**20(47.6%)**	**7(16.7%)**	**15(35.7%)**

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The study population comprised of 137 participants with a median age of 52 (IQR=25, 79) years with female predominance. These findings compare with a study in Kenya that indicated that most of the participants were female and the median age was 54.2 years (53). Studies have shown that women have better health seeking behavior than men(54). The screening and early diagnosis campaigns especially for breast cancer and cervical cancer is also a reason(55). Diagnosis of cancer was preponderant in patients above 60 years. This correlates with studies which indicated that the average incidence of cancer in lower middle income countries was 61.75 years(56). Cancer is one of the diseases promoted by tissue ageing(57).

Majority of the study participants had attained primary and secondary level education which may be attributed to the fact that there has been an increasing trend of primary school enrolment and the push by Kenyan government to have a 100% transition to secondary schools. This is further demonstrated by data from World Bank which indicated that the literacy rate in Kenya in 2021 was at 82%(58).

The most frequent cancer in this population was breast cancer (28.9%) followed by cervical cancer at 23%. Similar to a study in Kenya in 2019 which found that the most encountered cancer type was breast cancer at 27.8% followed by cervical cancer at 13%(63). Other findings estimated that breast cancer is the most commonly diagnosed cancer(64). This is accredited to the awareness campaigns and increased screening.

Stage IV disease was the most prevalent among the study participants at 35.6%. A study on the prevalence and determinants of late-stage presentation among cervical cancer patients estimated that the prevalence of late-stage presentation was 62.60% in Africa, 69.30% in Asia, 46.51% in Europe, and 50.16% in North America(65). This is due to many factors including lack of basic knowledge and awareness of identifying symptoms and misconceptions about the disease, barriers within the local primary healthcare providers, such as symptom mismanagement and delayed referrals, financial hardships, fear and stigma of cancer(66).

Liver disease and kidney failure were the most prevalent comorbidities among the study participants at 16.1% and 11.8% respectively. Prior studies identified liver cirrhosis as a major risk factor for primary liver cancer and increased risk of developing extra hepatic malignancies(67). A study in Ontario found that cancer incidence in the setting of kidney disease is substantial which increases with disease progression(68). Strategies to early detect and manage cancers associated with these patients are needed. Healthcare workers should be on the look to suspect and make correct diagnoses to avoid late stage conditions. With this knowledge, policy makers should aid in improving screening services in the health care facilities for early detection of cancer.

Doxorubicin and cyclophosphamide was the mostly used combination regimen among the study participants. This regimen is the first line, active and well tolerated in patients with metastatic breast cancer(71). The results are similar to a previous study at KNH which estimated that cyclophosphamide and doxorubicin combination was used at 14%(63).

The prevalence of thrombocytopenia was 31.4% among the study participants. In Ethiopia, the condition was estimated to be 8% (72), while in United states, it was estimated at 21%(30). In Kenya, thrombocytopenia was at 8% among CML patients on Imatinib (31). The findings of this study are comparable to a study in India that found the prevalence of the condition at 38%(73). Also, a recent study in Uganda found the occurrence of thrombocytopenia at 49% in a prospective observational study(74). The results suggest that this condition in cancer patients is a relevant problem in clinical practice.

With gender, TCP was more prevalent in women compared to men. This is similar to a Korean study which estimated that the prevalence of thrombocytopenia was significantly higher in females(76). This study further indicated that patients above 60 years had a higher prevalence. Many epidemiological studies have shown that the incidence of thrombocytopenia increases after age 60 years and peaks in patients over age 80 years(77). Cigarette smoking has been shown to significantly affect platelet morphological indices which affect its function. The prevalence of thrombocytopenia among participants with smoking history was 7.5%. In Thailand, a study found a bit

higher prevalence of thrombocytopenia among smokers at 13%(78). Further in this study, the prevalence of thrombocytopenia among alcohol consumers was at 4.5%. It is described that alcohol affects the production of thrombocytes and accelerates degradation and apoptosis of platelets(79). A study found that thrombocytopenia occurs in 3%–43% of healthy, well-fed alcohol-dependent people, 14%–81% of alcohol-dependent patients who require hospitalization and 25% of hospitalized alcohol-dependent patients(79).

The findings indicated that the prevalence of thrombocytopenia was high among hematological cancers at 55.8% compared to solid cancers at 44.1%. Previous studies further described that 10 - 38% of solid cancer patients and 40-68% of hematological cancer patients had thrombocytopenia (28). Among the hematological malignancies, thrombocytopenia was more prevalent in multiple myeloma at 8.8% followed by chronic lymphocytic leukemia at 4.4%. For solid cancers, the condition was more prevalent with breast cancer and cervical cancer followed by Lung cancer, colorectal cancer and esophageal cancer. Earlier studies found high prevalence in AML 33.4%, ALL 19.1%, aplastic anemia 13.6%, MDS 12.6% and multiple myeloma 9.4% among the hematological malignancies, while in solid tumors, colorectal cancer, lung cancer and ovarian cancer had high prevalence of thrombocytopenia (29). Bone marrow depression is a common feature in hematological malignancies or other bone marrow-involving cancers resulting in pancytopenia(80).

Thrombocytopenia was mostly encountered in patients with concomitant kidney failure at 21.3% while those with liver disease had a prevalence of thrombocytopenia at 14.9%. In Thailand, hypertension, diabetes mellitus, chronic kidney disease and liver cirrhosis were the most frequent concomitant conditions with high prevalence of thrombocytopenia(78). Thrombocytopenia is the most common hematologic abnormality seen in liver disease. The most notable contributor is portal hypertension, which leads to congestive splenomegaly and the sequestration of platelets in the spleen(81). Prolonged kidney impairment leads to decreased secretion of erythropoietin secretion by this organ which causes hematological changes such as anemia and thrombocytopenia.

The prevalence of thrombocytopenia among participants on radiotherapy was 14.0%. A previous study recorded 20% prevalence in patients exposed to radiation therapy(69).

There was however no statistical significant association between the two variables. Concurrent chemo radiation has been found to increase the risk of thrombocytopenia and lead to treatment interruptions(70)

The highest frequencies of thrombocytopenia were observed in patients on cyclophosphamide based combinations at 27.3%, carboplatin with paclitaxel combination at 16.2%, cisplatin based at 13.5% and oxaliplatin based combination at 10.8%. Previous findings in Netherlands indicated that highest prevalence of thrombocytopenia were observed in patients receiving carboplatin monotherapy (81.8%) and combination therapies that included carboplatin (58.2%), gemcitabine (64.4%), paclitaxel (59.3%) and oxaliplatin(28.6%)(82). Similarly, other studies demonstrated higher percentages of TCP in carboplatin monotherapy at 82%, oxaliplatin monotherapy at 50% while with combination therapy, carboplatin based therapies were at 58%, gemcitabine based chemotherapy at 64%, paclitaxel based regimens at 59% and oxaliplatin based chemotherapy regimens at 36%(30). These chemotherapeutic agents are associated with bone marrow depression leading to low blood cell counts.

Drug-induced immune thrombocytopenia (DITP) is a rare and often difficult-to-diagnose cause of thrombocytopenia, caused by drug-dependent platelet antibodies leading to increased platelet consumption and destruction. Drug-induced immune thrombocytopenia evolves within 7 days of initiation of the offending platelet (PLT) counts often start to recover 1 to 2 days after discontinuation of the offending medication. In this study, ceftriaxone was used by 23 participants within 7 days of the recorded laboratory values, none had thrombocytopenia. Some epidemiological studies conducted in Europe and United States reported that the annual minimum incidence is approximately ten persons per million(83)

Bivariate analysis to determine association of the socio demographic characteristics of participants and thrombocytopenia demonstrated that gender was significantly associated with thrombocytopenia (Crude OR=2.276, 95% CI, 1.064, 4.868 P=0.034). Results indicated that female participants had 2 times the odds to have thrombocytopenia compared to male participants. Recent studies have indicated that ITP occurs particularly

in women in their third or fourth decade, with an overall female to male ratio of 3 to 1. Sex hormones have been shown to play a role in the susceptibility of ITP(84).

Further, cancer type demonstrated a significant association with thrombocytopenia. Patients with hematological malignancies indicated to have 22 times the odds of having thrombocytopenia compared to solid malignancies (Crude OR=22.23, 95% CI, 7.523, 65.7 P=0.000). These are similar to previous findings which indicated highest prevalence of thrombocytopenia among hematological malignancies compared to solid malignancies 47% (95% CI 43%-51%), p<0.01(85). Hematological malignancies are associated with greater degree of bone marrow depression

There was a significant association between thrombocytopenia with cyclophosphamide based (P=0.002), carboplatin based (P=0.012), oxaliplatin based (P=0.002) and cisplatin based regimens (P=0.007). Other regimens which included ABVD, FOLFIRI and imatinib also indicated a significant relationship with thrombocytopenia (p=0.038). Local studies indicated that cyclophosphamide based regimens were associated with significant myelosuppression (p=0.007)(63). Other prevalence studies have shown that platinum based regimen combinations had significant associations with thrombocytopenia (p<0.001). These combinations are dexamethasone, cytarabine and cisplatin (DHAP), isophosphamide, carboplatin, etoposide (ICE), gemcitabine, dexamethasone, cisplatin (GDP), gemcitabine and oxaliplatin (34). With this knowledge available, constant monitoring of blood values is needed in patients who are on these high risk medications.

Multivariate analysis on the statistically significant variables to control confounders demonstrated that patients on carboplatin based regimen, which was a combination of carboplatin and paclitaxel was more likely to have thrombocytopenia compared to other regimens (adjusted OR=0.062, 95% CI, 0.007, 0.577 P=0.015). This was statistically significant. Previous studies had indicated that patients on carboplatin based and paclitaxel based combinations had a higher risk of thrombocytopenia (30). A study in Indonesia on paclitaxel-carboplatin chemotherapy induced hematologic toxicities among epithelial ovarian cancer patients, demonstrated that this combination had a significant association with thrombocytopenia (p<0.001)(86).

Significant association was also identified with the type of cancer, where patients with hematological malignancies had 0.02 times the odds of having thrombocytopenia compared to those with solid malignancies (p=0.015). This has been illustrated by earlier studies showing significant association with bone marrow depression causing low blood cells production leading to cytopenias (79).

Participants with mild thrombocytopenia (100,000-150,000/µL platelets) were 47.6%, while 16.7% had moderate disease (50,000-99,000/µL platelets) and 35.7% had severe thrombocytopenia (<50,000/µL platelets). Most of the participants had mild thrombocytopenia similar to previous studies which indicated similar findings (45). Management strategies employed in the present study are no intervention (50%), of whom the majority were patients with mild thrombocytopenia (45.2%), platelets transfusion at 47.7% mostly among the severe cases of thrombocytopenia (28.6%) and chemotherapy dose delay at 2.3% which was one patient with severe thrombocytopenia.

These findings correlate with previous studies which have shown that platelets transfusion is generally instituted in severe cases of thrombocytopenia <10,000/ µL or when there is an active bleeding. Patients with platelet counts <50,000/µL have higher rates of any bleeding (49). Majorly, close monitoring of the patients is done with mild and moderate thrombocytopenia. Drugs like gemcitabine or oxaliplatin can cause immune mediated thrombocytopenia, which should be discontinued on suspicion. For dose-dependent thrombocytopenia, a dose reduction has been shown to be sufficient (49). Unfortunately decreasing relative dose intensity is associated with reduced tumor response and remission rates

Thrombopoietic growth factors (recombinant human thrombopoietin, pegylated human megakaryocyte growth and development factor, romiplostim, eltrombopag, avatrombopag and hetrombopag) improve pretreatment and nadir platelet counts, reduce the need for platelet transfusions, and enable chemotherapy dose intensity to be maintained. National Comprehensive Cancer Network guidelines permit their use but their widespread adoption awaits adequate phase III randomized, placebo-controlled studies demonstrating maintenance of relative dose intensity, reduction of platelet transfusions and bleeding, and possibly improved survival. Their potential appropriate

use also depends on consensus by the oncology community as to what constitutes an appropriate pretreatment platelet count as well as identification of patient-related and treatment variables that might predict bleeding(87)

5.2 Study limitations

The data gathered for this study depended on information on the participants' files. Some of the files lacked some information like the cancer stages. This was minimized by thoroughly perusing the patient files and based on other recorded clinical information about the disease spread; a stage of the disease was concluded. For instance, patients with cervical cancer with chest scans showing spread of the disease to the lungs indicate a stage IV disease.

5.3 Delimitations

The findings of the study may not be generalizable because the study only focused on patients who attended KNH cancer treatment center, with the inclusion of those who meet the eligibility criteria. However, most patients across the country seek cancer treatment services at Kenyatta National Hospital.

5.4 Conclusion

The results suggest that thrombocytopenia in cancer patients is a relevant problem in clinical practice. Our findings support the need for regular assessment of platelet count levels to identify cancer patients at risk of serious clinical outcomes. The study identified participants with hematological malignancies and those on carboplatin based regimens as the most likely to have thrombocytopenia.

Most of the participants had mild thrombocytopenia of which there was no intervention given. Those with moderate and severe thrombocytopenia received platelets transfusion as the main intervention.

5.4 Recommendations

Healthcare workers need to be aware that thrombocytopenia is a common occurrence in certain group of cancer patients. Patients on carboplatin based regimens and those with

hematological malignancies are more likely to have thrombocytopenia, and regular monitoring of platelet levels is of essence.

Continuous medical education (CME) is necessary for healthcare workers attending to cancer patients to be aware of these risk factors. The CME will also help clinicians to know the best approach in cancer patients with thrombocytopenia. For example, in immune-mediated thrombocytopenia the drug must be avoided, while in dose-dependent thrombocytopenia a dose reduction may be sufficient.

Screening services should be increased to detect cancer in its early stages as most patients are diagnosed in late stages which are associated with complications like thrombocytopenia.

A standard approach for the management of thrombocytopenia should be put in place which will enable all those attending to cancer patients to identify thresholds and institute the necessary strategies.

CHAPTER 6: REFERENCES

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APPENDIX

APPENDIX A: ELIGIBILITY CHECKLIST

CRITERIA	Yes	No
1. Adult Cancer patient ≥18years	☐	☐
2. Undergoing cancer treatment at KNH	☐	☐

Give reasons if patient is excluded:

☐ Patient has incomplete records

☐ Other. If other, specify reason for exclusion

……

……

……

……

APPENDIX B: DATA COLLECTION FORM

DATE OF DATA COLLECTION:……

CODE:……

PART 1: PARTICIPANT'S BIODATA

Date of birth: Date……Month…...Year……

Age (in years) at diagnosis of cancer.....

Gender: 0 ☐ Male 1 ☐ Female

Weight (in Kgs):…….

Height (in meters):……

Area of residence: 0 ☐ Urban 1 ☐ Rural

County……..

Level of education: 0 ☐ Primary 1 ☐ Secondary 2 ☐ Tertiary

3 ☐ Did not attend school

Occupation: 0 ☐ Unemployed 1 ☐ Self-employed 2 ☐ Employed

Marital status: 0 ☐ Single 1 ☐ Married 2 ☐ Divorced 3 ☐ Separated

4 ☐ Widow/Widower

Does participant smoke: 0 ☐ Yes 1 ☐ No

Does participant take alcohol: 0 ☐ Yes 1 ☐ No

PART 2: CLINICAL CHARACTERISTICS

Type of cancer patient has been diagnosed with

Cancer type	**Tick appropriately**
Acute myeloid leukemia	
Acute lymphoblastic leukemia	
Chronic lymphocytic leukemia	
Chronic myelogenous leukemia	
Hodgkin's Lymphoma	
Non- Hodgkin's Lymphoma	
Colorectal cancer	
Lung cancer	
Ovarian cancer	
Breast cancer	
Prostate cancer	
Cervical cancer	
Esophageal cancer	
Bone cancer	
Endometrial cancer	
Melanoma	
Pancreatic cancer	
Others(specify)	

Cancer stage: ☐ I ☐ II ☐ III ☐ IV

☐ M1 ☐ M2 ☐ M3 ☐ M4

☐ L1 ☐ L2 ☐ L3 ☐ L4

☐ Not staged

Concomitant conditions the patient has:

Condition	Diagnosis	Tick as appropriate	Duration
Liver disease	**Liver biopsy……..☐** **or** **Imaging (ultrasound/CT scan)☐** **or** **Elevated AST and ALT……☐**		
Kidney failure	**Increase of serum creatinine…☐** **or** **Decrease in GFR……☐** **or** **Urine output <0.3 ml/kg per h☐** **or** **Anuria for >12 h……☐**		
Thyroid disorders	**T4 levels <5.0 or>11.0 ug/dL ..☐**		
Deep vein thrombosis	**Confirmed by imaging…….☐**		
Sepsis	**Elevated WBCs ……☐** **and** **SOFA score ≥2……☐**		
HELLP syndrome	**Serum bilirubin ≥1.2 mg/dL…☐** **Anemia (HB<10g/Dl) …….☐** **Elevated AST or ALT …….☐** **and** **Low platelets: <100,000 /uL…☐**		
Other(specify)			

Use of other medications:

Medication	**Within the last 7 days**	**More than 7 days**	**Duration of treatment**
Heparin			
Quinine			
Vancomycin			
Penicillin			
Rifampin			
Carbamazepine			
Ceftriaxone			
Ibuprofen			
Mirtazapine			
Oxaliplatin			
Suramin			
GP IIb/IIIa inhibitors (eftifibatide)			
Suramin			
Platelet transfusion			
Others (specify)			

PART 3: CANCER TREATMENT MODALITIES

Chemotherapeutic agents patent is on:

……
……
……
……
……
……..

Is patient on radiotherapy? 0 ☐ Yes 1 ☐ No

PART 4: PREVALENCE OF THROMBOCYTOPENIA

Baseline cell counts (At admission)

Platelets……

Hemoglobin……..

Neutrophils……

Did the patient develop thrombocytopenia within the study period?

☐ Yes ☐ No

If the yes, indicate platelets level at the diagnosis of thrombocytopenia

……
……

Severity of thrombocytopenia

☐ Mild ☐ Moderate ☐ Severe

PART 5: INTERVENTIONS FOR THROMBOCYTOPENIA

Intervention	**Tick appropriately**
Platelets transfusion	
Chemotherapy dose delay	
Chemotherapy dose adjustment	
Change of treatment	
Discontinuation with therapy	
No intervention	
Other(specify)	

APPENDIX C: KNH-UON ERC APPROVAL LETTER

UNIVERSITY OF NAIROBI
FACULTY 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

Ref.No.KNH/ERC/Mod&SAE/97

15th May, 2023

Vitalis Kiplagat Kiptoo
Reg. No. U56/38319/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear Vitalis,

Re: Approval of Modifications - study titled, "Risk factors and management of thrombocytopenia among adult patients receiving cancer treatment for hematological and solid cancers at Kenyatta National Hospital" (P817/10/2022)

Your communication dated 22nd April, 2023 refers.

The KNH- UoN ERC has reviewed and **approved** the following modifications made to the study:

1. Revision of study title from 'Risk factors and management of thrombocytopenia among adult patients receiving chemotherapy for hematological and solid cancers at Kenyatta National Hospital' to "***Risk factors and management of thrombocytopenia among adult patients receiving cancer treatment for hematological and solid cancers at Kenyatta National Hospital***".
2. Revision of one study objective (and research question) from 'To estimate the *incidence* of thrombocytopenia among adult cancer patients undergoing chemotherapy at KNH' to "*To estimate the **prevalence** of thrombocytopenia among adult cancer patients undergoing chemotherapy at KNH*".
3. Change of study population from those receiving chemotherapy to '***those receiving cancer treatment***'.

The requested modifications have been adequately justified and are incorporated in the revised research proposal. No further risk to participants is anticipated.

With this approval; the following have been endorsed and revised data collection tool stamped for use:

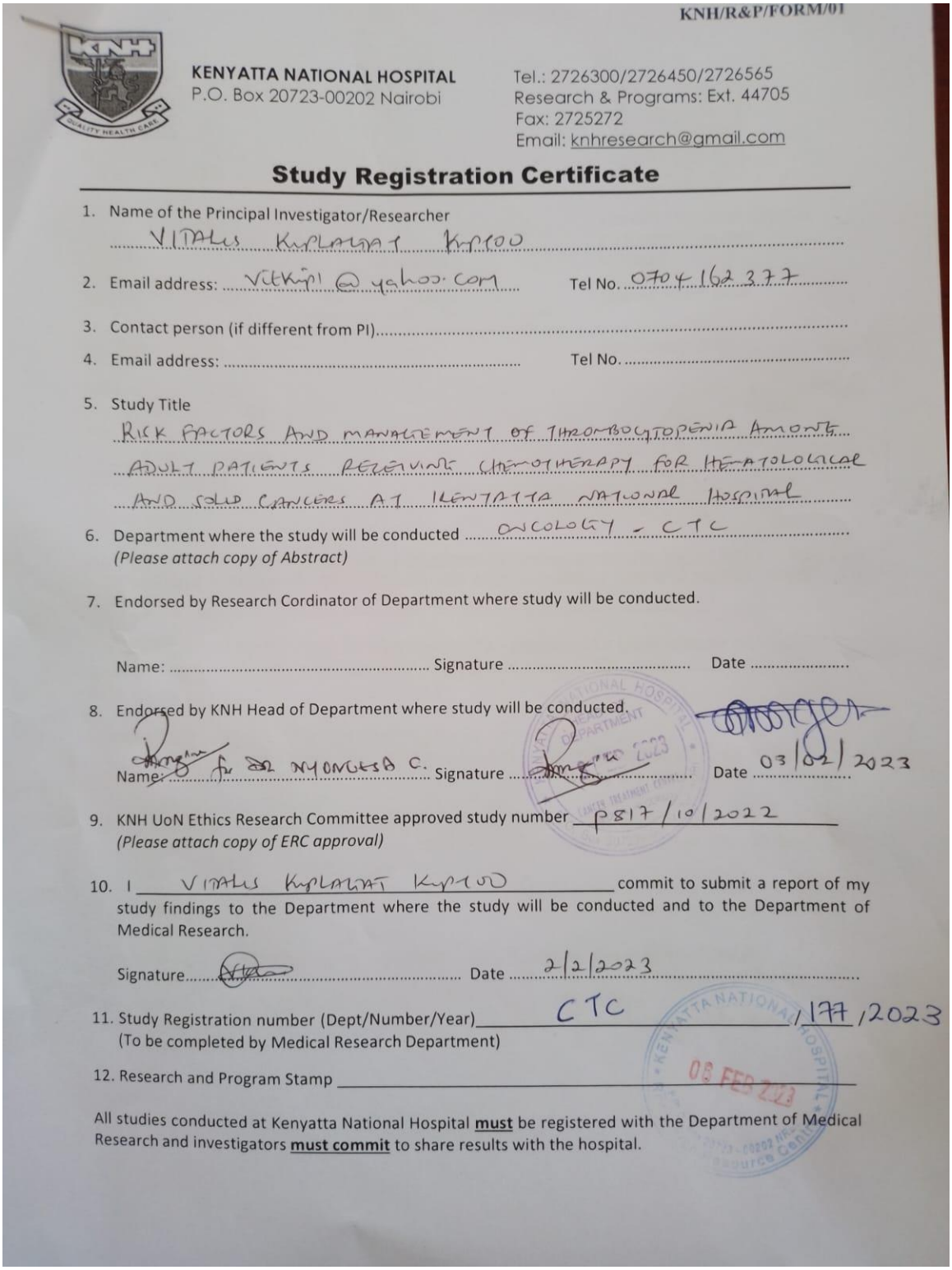
i. Revised research proposal.
ii. Revised Data Collection Form.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH- UoN ERC

cc. The Dean, Faculty of Health Sciences, UoN
The Senior Director, Clinical Services, KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Pharmacy, UoN
Supervisors: Dr. Sylvia Opanga, Dept. of Pharmacy, UoN
Prof. Faith Okalebo, Dept. of Pharmacy, UoN

APPENDIX D: INSTITUTIONAL APPROVAL



KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
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Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   VITALIS KIPLAGAT KIPROO
2. Email address: vitkip1@yahoo.com Tel No. 0704 162 377
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   RISK FACTORS AND MANAGEMENT OF THROMBOCYTOPENIA AMONGST ADULT PATIENTS RECEIVING CHEMOTHERAPY FOR HEMATOLOGICAL AND SOLID CANCERS AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted ONCOLOGY - CTC
   (Please attach copy of Abstract)
7. Endorsed by Research Cordinator of Department where study will be conducted.

   Name: ..... Signature ..... Date .....
8. Endorsed by KNH Head of Department where study will be conducted.

   Name: ..... Signature ..... Date 03/02/2023
9. KNH UoN Ethics Research Committee approved study number P817/10/2022
   (Please attach copy of ERC approval)
10. I VITALIS KIPLAGAT KIPROO 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..... Date 2/2/2023
11. Study Registration number (Dept/Number/Year) CTC /177/2023
    (To be completed by Medical Research Department)
12. Research and Program Stamp

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.