
**College of Health Sciences**

**School of Pharmacy**

**Department of Pharmacology and Clinical Pharmacy**

# Thromboembolic Events Among Cancer Patients Treated with Chemotherapy at Adult Oncology Unit of Tikur Anbessa Specialized Hospital: A Retrospective Study

**By: Abdella Birhan (BPharm)**

**March 2020**

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**By: Abdella Birhan (BPharm)**

**A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the Requirements of Master of Science Degree in Pharmacy Practice.**

**Under the supervision of: Shemsu Umer (Ph.D.) and Wondemagegnhu Tigneh (MD, Oncologist)**

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**Addis Ababa University**

**School of Graduate Studies**

This is to certify that the thesis prepared by Abdella Birhan, entitled with: Thromboembolic Events Among Cancer Patients Treated with Chemotherapy at Adult Oncology Unit if Tikur Anbessa Specialized Hospital: A Retrospective Study. Submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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**Abstract**

**Thromboembolic Events Among Cancer Patients Treated with Chemotherapy at Adult Oncology Unit of Tikur Anbessa Specialized Hospital: A Retrospective Study**

**Abdella Birhan, Addis Ababa University, 2019**

Venous thromboembolism is a common problem in patients treated for cancer, although the reported incidence varies widely between studies. Unlike other countries, in Ethiopia to our knowledge no such studies had been done yet and the findings of this study will assist treatment decisions in adult patients treated at the oncology unit of Tikur Anbessa Specialized Hospital. Hence, this study was aimed to assess the incidence of thromboembolic events events among cancer patients treated with chemotherapy and their characteristics. An institution-based retrospective cross-sectional study was conducted from 1st March, 2019 to 1st June, 2019. Data were collected retrospectively from a total of 423 patient medical records. Patients who have received at least a single cycle of any chemotherapy regimen was included in the study. Systematic random sampling technique was employed to recruit the study participants. The data were entered into Epi-info version 7 and then exported to and analyzed using Statistical Package for Social Sciences, version 25. Descriptive statistics were used to summarize the data while binary logistic regression analysis was used to determine factors associated with the risk of thromboembolic events among cancer patients treated by chemotherapy. *P*-value <0.05 was considered as statistically significant. The median age of study participants was 43 years, which ranged from 14 to 83 years. Majority of the study participants were treated for breast cancer. Thromboembolic events encountered in 43 (10.2 %) of patients, from which the commonest one being deep venous thrombosis 36 (85.7 %), followed by myocardial infarction 5 (11.9 %), and pulmonary embolism 1 (2.4 %). In multivariable logistic regression, blood transfusion, a primary site of cancer with gastrointestinal malignancy and performance status showed statically significant association. The incidence of thromboembolic events among cancer patients who had been treated by chemotherapy was high compared to other studies. Hence, other prospective randomized trials are needed to see the importance of thrombo-prophylaxis in such high-risk patients.

**Key words**: Cancer, Thromboembolic events, Venous Thromboembolism, Chemotherapy.

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**Abbreviation and acronyms**

| | |
|---|---|
| AT | Arterial Thrombosis |
| BMI | Body Mass Index |
| CI | Confidence interval |
| CVC | Central Venous Catheter |
| DVT | Deep Venous Thrombosis |
| ECOG | Eastern Cooperative Oncology Group |
| 5-FU | 5-Fluorouracil |
| FOLFORI | 5-FU, Folinic Acid and Irinotecan |
| FOLFOX | 5-FU, Folinic Acid and Oxaliplatin |
| GCSF | Granulocyte Colony Stimulating Factors |
| LMWH | Low Molecular Weight Heparin |
| MI | Myocardial Infarction |
| PE | Pulmonary Embolism |
| TASH | Tikur Anbessa Specialized Hospital |
| TE | Thromboembolism |
| VTE | Venous Thromboembolism |
| WBC | White Blood Cell |

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# 1. Introduction

## 1.1. Background

Cancer is a group of diseases characterized by the abnormal growth of cells. When the growth is not well controlled, it disseminated to different sites in the body (Sm *et al.*, 2016). In developed nations, it is the 2nd most common cause of death only next to cardiovascular diseases. Epidemiological reports indicated that the emergence of cancer becomes similar in developing nations as well (Kifle *et al.*, 2016). Currently, treatment modalities for cancer incorporate surgery, systemic therapies and radiotherapy. They can be given alone or in combination and either with the curative or palliative purpose (Camacho *et al.*, 2014).

Most cancer treatment options have been shown to increase the risk of venous thromboembolism (VTE), in addition to other risk factors. These include prolonged hospitalization, central venous catheters (CVC), type of malignancy, cancer stage and supportive therapies such as blood transfusion (Meinardi *et al.*, 2005). VTE is common in cancer patients, although the reported incidence varies widely between studies. Thromboembolic (TE) events can be classified into deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial events, like stroke and myocardial infarction (MI) (Khorana, 2011). These events are significant contributors to morbidity and mortality in these particular patients (Maraveyas *et al.*, 2011).

Multiple risk factors for VTE have been identified in patients with cancer. The risk factors are categorized either as patient characteristics or malignancy-related characteristics, including specific therapeutic intervention (Gallus *et al.*, 2013), the biology of cancer itself, surgeries and invasive procedures (Abdel-Razeq *et al.*, 2017). Most studies suggested that solid malignancies such as pancreatic, lung, colon, ovarian, primary hepatic and brain cancer are associated with an increased risk of TE (Barni *et al.*, 2011).

Yet, it is not clear which chemotherapeutic agent is associated with a higher risk of VTE compared with other risk factors. However, cisplatin-based regimens particularly have been associated with a wide range of VTE complications (Falanga and Marchetti, 2012). Anthracyclines and fluoropyrimidines are other agents mostly associated with TE events. The other study indicated that these agents were significantly associated with VTEs. Simultaneous

use of steroids, erythropoietin, and granulocyte colony-stimulating factors (GCSF) have also been associated with an increased incidence of TEs (Barni *et al.*, 2011).

Several explanations are available on how these chemotherapies are associated with VTE. These include direct damage to the vascular endothelium, enhancement of pro-coagulant activity, reduction of anticoagulation production, platelet activation and aggregation and vascular inflammation (Zahir *et al.*, 2017).

Patients treated for cancer have several-fold higher risk of developing TE compared with the general population, with relative risks ranging from 4 to 7 (Timp *et al.*, 2018). The estimated annual incidence of TE in these group of patients is 0.5%, and it is one of the leading cause of death (Khorana *et al.*, 2018). Most studies indicated that the survival rate of patients treated for cancer and developing VTE is significantly lower compared to patients without such complications (Abdel-razeq *et al.*, 2018). Cancer diagnosed at the same time as or within one year after an episode of VTE is associated with an advanced stage of cancer and a poor prognosis (Ørensen *et al.*, 2000).

The occurrences of VTE are higher in African-Americans than other population subgroups. It was estimated that the risk is over five times more than Asian populations. The risk is intermediate for European and Hispanic populations (Mcclure. and Zakai., 2011). Currently, there is a growing concern about TE events in patients treated by several chemotherapy regimens. This study is critical because a significant number of patients may benefit from early detection and use of thrombo-prophylaxis for TE events despite underestimation of those incidents.

Hence, this study was aimed to assess the incidence and characteristics of TE events among cancer patients treated with chemotherapy and their characteristics. Such continued researches can assist in planning interventions and improve patient treatment outcomes.

## 1.2. Statement of the problem

Even if most patients endure TE events, above 1/3$^{rd}$ of patients will suffer from severe and long-term complications, such as venous stasis syndromes expressed by chronic dependent leg edema, ulcers and painful swelling and some of them may also develop chronic complication like pulmonary hypertension (Gallus *et al.*, 2013; Moore. *et al.*, 2011).

Chemotherapeutic agents are highly associated with thrombosis complications, which can occur as both arterial and venous thrombosis. One retrospective study revealed that platinum-based regimens were significantly associated with VTE events, and the rates were higher with cisplatin-compared to oxaliplatin-based therapy (Honecker *et al.*, 2013). In another study conducted on patients with urothelial cancer, 12.9% of patients receiving chemotherapy experienced TE events and the developed TEs resulted in death in three of the patients who have received the therapy (Anders, Grigsby and Singh, 2006). The results of a similar retrospective study of patients with germ cell cancer receiving chemotherapy showed that 8.4% of patients experienced TE events, with one case of death report. Additionally, a prospective study of 108 patients with stage III to IV non–small-cell lung cancer treated with cisplatin and gemcitabine showed that 17.6% of patients experienced a TE event; and four patients died as a result of the TE event (Moore *et al.*, 2011).

To decrease the impact of VTE in patients taking chemotherapy, identifying cancer patients at highest risk is vital for the appropriate interventions such as thrombo-prophylaxis (Khorana *et al.*, 2016). Most patients with cancer treatment need thrombo-prophylaxis throughout their hospital stay. However, for all patients with cancer, the use of anticoagulant is not recommended, especially in an outpatient setting. For selected high-risk patients, its use may be considered. Either low–molecular weight heparin (LMWH) or low-dose aspirin can be used as prophylaxis in selected patients (Lyman *et al.*, 2019).

Several studies implicated, genetics difference is also one of the contributing factors for the occurrence of TE event (White and Keenan, 2009; Mcclure. and Zakai., 2011; Moore *et al.*, 2011; Zakai *et al.*, 2014; Crous-Bou, Harrington and Kabrhel, 2017). Unlike other countries, in Ethiopia no such studies had been done yet, and findings of this study will assist treatment

decisions in adult patients treated at the oncology unit of Tikur Anbessa Specialized Hospital (TASH).

### 1.3. Significance of the study

Now a days, there is a considerable concern about undesirable effects associated with chemotherapy utilization. Among these TE events are one of the deteriorating consequences of chemotherapies. However, not enough attention is given to these unwanted effects. Thus, the result of this study is crucial to identify the correlation between TEs and chemotherapeutic agents and hence, large number of patients will be benefited from early identification and use of preventive thrombo-prophylaxis towards TE events.

If it is possible to anticipate the occurrences of TE event associated with the use of a chemotherapeutic regimen, it would be rational for developing strategies in tackling possible events. It has beneficiary clinical and economic outcomes in patient care service by reducing mortality, morbidity, hospitalization, treatment costs and also improving patient's quality of life.

Moreover, if it is found that the incidence of TE is higher among our society, possible recommendations will be forwarded to the responsible bodies and all stakeholders in order to prevent/reduce undesired events associated with the development of TE events. Educational or training sections to health care providers will also be organized to create awareness about the occurrences of these chemotherapy related TEs.

Furthermore, the findings of this study helps in identifying predictive factors related to TE events of chemotherapy. This study will also motivate other researchers to dedicate their efforts in related subjects and can be a useful input for further investigations. The findings of this study will help to identify the incidents and characteristics of thrombosis in adult patients treated at the oncology unit of TASH.

## 2. Literature review

Cancer is a collective term used to describe a condition in which the body's cells starts to grow and replicate uncontrollably. These cells can enter and annihilate healthy tissue (Kifle *et al.*, 2016). Most treatment alternatives increase risk of TE events, particularly chemotherapy associated with a higher risk (Connolly and Francis, 2013). TE events due to chemotherapies constitute a significant concern. The incidence of VTE in hospitalized patients receiving chemotherapy is around 5.7% (Key *et al.*, 2019). Several controlled clinical trials of systemic chemotherapy use in women with breast cancer have shown a clear association between chemotherapy and increased incidence of VTE. A prospective study of nearly 4,500 patients receiving outpatient chemotherapy reported a 2.7-fold increase in arterial thrombosis, and a 47-fold increase in the mortality rate from VTE compared with the general population (Abdel-Razeq *et al.*, 2017).

The pathophysiology of coagulation in cancer is complex and multifactorial. However, a unique feature in malignancy is the role played by the expression of tumor cell-associated clot promoting properties (Falanga and Marchetti, 2012). These properties lead to the activation of the clotting cascade, with the generation of thrombin and fibrin, and the stimulation of platelets, leukocytes and endothelial cells which expose their cellular procoagulant features (Lechner *et al.*, 2007). Several of these mechanisms can contribute to tumor development and progression (Falanga, Marchetti and Vignoli, 2013), although a clear connection with thrombosis remains to be established. Vascular toxicity, which is endothelial cell injury, was observed in association with platinum-based chemotherapy and is considered to be another pathological mechanism. Cytotoxicity in both cancer cells and non-malignant cells is thought to be a consequence of apoptosis caused by Cisplatin (Lechner *et al.*, 2007).

Studies reveal that TE events are the major leading cause of death in cancer patients. Patients with cancer who had TE events do not have good prognosis compared with their counterparts. Patients with cancer-associated TE events have higher risks of coagulation complications. Moreover, the risk of recurrence is higher in these group of patients (Timp *et al.*, 2018). There is a shred of evidences that show treatment with chemotherapeutic agents increases this risk to a great extent (Honecker *et al.*, 2013). These events may be more aggravated by some agents compared to the others and this has been observed in patients receiving adjuvant chemotherapy

for several types of malignancies (Piotr, Malcolm and Ian, 1998). For instance, anti-cancer drugs for testicular cancer has been associated with both acute and long-term vascular toxicity (Meinardi *et al.*, 2005).

The association between chemotherapy and TE events has been examined most broadly in patients with breast cancer. In one study, among 205 patients randomly assigned to chemotherapy treatment, 14 episodes of TE events occurred during 979 patient-months of chemotherapy. In comparison, there were no such events occurred during 2413 patient-months in patients without chemotherapy (Barni *et al.*, 2010). Gynecologic malignancies are also other type of cancers that are associated with an increased risk of VTE (Honecker *et al.*, 2013).

Direct cause and effect relationship between L-asparaginase treatment and increased thrombogenic risk were also reported. High dose of steroids was associated with a 3.5-fold increase in the odds of developing VTE (Honecker *et al.*, 2013). Hormonal therapy has also been indicated to increase VTE risk in patients with breast cancer. In Studies  showed that selective estrogen receptor modulator (tamoxifen) had a 1.5–7.1-fold increase in the risk of VTE compared with placebo (Falanga and Marchetti, 2012).

The incidence of VTE varies with race; African-Americans had higher risk than Asian populations whereas, European and Hispanic populations are at an intermediate risk for developing TE (Mcclure. and Zakai., 2011). The incident is much higher, particularly following exposure to a provoking risk factor such as surgery, medical illness, trauma or chemotherapy (Barni *et al.*, 2010). The DVT and PE are more pronounced in African-Americans compared to Caucasian and other racial groups and Asians/Pacific Islanders have a much lower prevalence of VTE (Zakai *et al.*, 2014). Hispanics have a significantly lower prevalence of VTE compared to Caucasians, but higher than Asians/Pacific Islanders. The incidence of recurrent VTE varies depending on gender, type of TE event and race (White and Keenan, 2009).

Economic burden of TE events are due to lengthy hospitalization, with a mean estimated cost of greater than $20,000. This economic burden is probably an underrate because around $1/4^{th}$ of patients with cancer who have TE events probably need to be re-hospitalized because of complications and these recurrent of TE event (Moore *et al.*, 2011).

In one population based study on TE risk factors in total of 625 cancer patients, the disease by itself was appeared to increase the risk of TE events almost 4-folds however, patients with cancer and took chemotherapy increase the risk up to 6.5-folds. This study indicated the presence of an indwelling CVC as a significant risk factor for the development of VTE. However, radiotherapy has not been proven to increase the risk of VTE complications (Falanga and Marchetti, 2012).

In a retrospective review of 253 patients with ovarian cancer treated with surgery and chemotherapy in Italy between 1990 and 2001 revealed a 16.6% rate of VTE. Multivariate analysis demonstrated that residual disease, increasing age and body mass index (BMI) were independent risk factors for the development of VTE. In 2007, investigators also reported that, among 13,031 cases of ovarian cancer diagnosed in California between 1993 and 1997, there was a 5.2% rate of VTE within 24 months of diagnosis. Development of VTE was a predictor of reduced survival (Barni *et al.*, 2010).

In a cohort study in the Netherlands, tumors of the bone, ovary, brain and pancreas were found to be associated with the highest incidence of VTE. Patients with distant metastases had a 1.9-fold increased risk. Chemotherapy leads to a 2.2-fold increased risk, and hormonal therapy leads to a 1.6-fold increased risk compared with patients not using these treatment modalities. On the contrary patients with radiotherapy or surgery does not show an increased risk (Blom *et al.*, 2006).

A review done in Australia by 2016 showed that, among patients with esophageal and gastric cancer, the incidence of VTE ranged from 4 to 19%. Gastric cancer and Stage III or IV disease identified as risk factors for developing VTE. Neoadjuvant chemotherapy identified as an independent risk factor for developing VTE. Symptomatic and asymptomatic VTE has shown a similar effect on mortality. Median overall survival for asymptomatic VTE was 13.9 months versus 12.8 months if the VTE was symptomatic (Bright *et al.*, 2016).

In a multi-institutional retrospective analysis of 761 patients with muscle-invasive bladder cancer who underwent neoadjuvant chemotherapy, the Khorana score indicated an intermediate TE event risk in 88% of the patients. The overall incidence of TE events in patients undergoing neoadjuvant chemotherapy was 14% with a wide variation of 5% to 32% among institutions. Patients with TE events were older and received a longer neoadjuvant chemotherapy course

compared to patients without a TE event. Of the TE events, 58% developed preoperatively, and 72% were symptomatic. On multivariable regression analysis, the development of a TE event was not significantly associated with decreased overall survival. However, pathological stage and a high Khorana score were adverse risk factors for overall survival (Duivenvoorden *et al.*, 2016).

A retrospective study done in Manchester showed that in a total of 52 patients, 9% and 4% of them had VTE and Arterial Thrombosis (AT) event respectively. Of those patients with VTE events, 39 had PE and 13 DVT. Whereas in patients with AT events: 7 of the patients developed MI and 8 of them developed limb ischemia. Additionally, 4 patients developed cerebrovascular accidents and 3 patients developed superior mesenteric artery thrombosis (Papaxoinis *et al.*, 2018).

A similar retrospective study in Feinberg revealed that from 128 participants, 17 had reported TE events during the time they were on first-line chemotherapy. 9 patients had a PE, and 8 had a DVT. The mean BMI in the group that developed VTE was 28, and in the group without VTE, it was 26.5. On multivariate analysis, patients who developed VTE had significantly longer postoperative hospital stays (7 vs. 5 days, retrospectively) and lower rates of complete response (Pant *et al.*, 2014).

Another single institution retrospective cohort review of 271 patients treated with multiple chemotherapy regimens, vascular events occurred in 35 patients. In 17 patients, the presenting vascular event was DVT in an extremity. Of these patients, three also had clinical signs of PE. From those patients, six presented with PE, including one who demonstrated clinical signs of DVT and 6 with acute or sub-acute arterial occlusion. Patients with DVT and or PE (74%) had events in the first 2 cycles of treatment, which constituted 53% of all cycles given, with a range of 3 to 45 days (median 16) from start of the chemotherapy cycle to diagnosis of the vascular event (Piotr, Malcolm and Ian, 1998).

A retrospective study from Michigan State University, United States of America (USA), reviewed 932 patients, in 2011. From those 169 patients developed TE events within four weeks of their last chemotherapy dose. The majority of events were DVTs alone (n=84), followed by PEs alone (n=43), DVT plus PE (n=23), arterial thrombosis alone (n=14), and DVT plus an

arterial thrombosis (n=5). Ninety-five events were symptomatic and 74 found incidentally. It considers that most, if not all, events would warrant therapeutic intervention (Moore *et al.*, 2011).

A hospital-based retrospective cross-sectional study done in Jordan assessed 1677 patient records, treated with combined chemotherapy regimens. TE events reported in 110 of them, and the highest was in patients with gastric cancer (20.9%) and the lowest in patients with lymphoma (1.6%). VTE events included DVT in 69 (62.7%), PE in 18 (16.9%) and arterial thrombosis in 17 (15.6%). A majority (51.1%) of the patients had stage IV disease and only 16% had stage I or II. In a multivariate analysis, significantly higher rates of VTE were associated with gastric as the primary tumor, advanced-stage disease, female sex but not age and the Khorana risk score or type of cisplatin regimen (Abdel-razeq *et al.*, 2018).

A prospective cohort study in Pakistan indicated that among 200 patients who had received Cisplatin-based chemotherapy, the crude relative risk of VTE in the Cisplatin group was almost 3 times higher than in the Non-Cisplatin group. When adjusted by gender, Eastern Cooperative Oncology Group (ECOG) status, GCSF, presence of CVC and Khorana risk score. The adjusted relative risk (RR) of VTE in patients treated by Cisplatin based chemotherapy was 3.3 times higher than patients treated by non Cisplatin based regimens. Among the VTE events, most were DVTs, which is 18 in the cisplatin group while 7 in a non-cisplatin group. From those who suffered a VTE event, four died in the cisplatin group while one in a non-cisplatin group (Zahir *et al.*, 2017).

**Table 1: Eastern Cooperative Oncology Group performance status.**

| Grade | ECOG performance status |
|---|---|
| Zero | Patients fully active, able to carry on all predeceased performance without restriction |
| One | Patients with restrictions in physical activity but ambulatory and able to carry out any work activities. |
| Two | Patient with ambulatory and capable of self-care but unable to carry out any work activities: up and about more than 50% of waking hours. |
| Three | Patients capable of only limited self-care: confined to the bed or chair more than 50% of walking hours. |
| Four | Patients with a complete disability; cannot carry any self-care activities; totally confined to the chair or bed. |
| Five | Patients who died due to cancer |

A study analyzed 193 patients, who were being treated for a different type of malignancy by platinum-based chemotherapy in Hamburg, Germany, between 2000 and 2009. VTE events detected in 22 patients; however, in 18 of these 22 patients experienced VTE events before initiation of chemotherapy, 12 of them at primary diagnosis and six at first relapse. No patient developed a VTE event in the interval between completion of chemotherapy and final tumor staging 4–6 weeks later. All patients experiencing a VTE event during chemotherapy received cisplatin-based treatment (Honecker *et al.*, 2013).

A systematic review and meta-analysis conducted in New York, USA, in the review among a total of 8216 patients, 4154 of them were on Cisplatin and 4062 of them were on non Cisplatin. In the Cisplatin group, 34 patients experienced AT compared with 21 patients in the non-cisplatin group and the overall incidence of AT in patients receiving Cisplatin-based

chemotherapy was 0.67%. The RR of AT for Cisplatin-based versus non-Cisplatin-based chemotherapy was 1.36 (Proverbs-singh *et al.*, 2012).

Another systematic review and meta-analysis done in Baylor College of Medicine, Houston, USA, in 2012 showed that among a total of 8,216 patients with various advanced solid tumors from 38 randomized controlled trials showed that the incidence of VTEs were 1.92% in patients treated with Cisplatin-based chemotherapy and 0.79% in patients treated with non– Cisplatin-based regimens. Patients receiving cisplatin-based chemotherapy had a significantly increased risk of VTEs with RR ratio of 1.67 (Seng *et al.*, 2012).

A report from USA, in 2009, compared to all other racial groups; African Americans had the highest standardized incidence of both idiopathic and secondary VTE. The incidence of secondary VTE in African Americans was 107 events/100,000/year compared to 75 events/100,000/year among Caucasians. Another interesting finding was that a higher proportion of the VTE events in African Americans diagnosed as PE which accounted 36% of all of their VTE events. It was 32% in Caucasians and only 26% for Hispanics (White and Keenan, 2009).

## 3. Objectives

### 3.1. General objective

- ✓ To determine the incidences of TE events among cancer patients treated with chemotherapy and their characteristics at the oncology unit of TASH, Addis Ababa, Ethiopia.

### 3.2. Specific objectives

- ✓ To determine the incidences of TE events in patients with cancer who received chemotherapy.
- ✓ To determine characteristics of thrombosis in patients with cancer who received chemotherapy.
- ✓ To identify predictive factors associated with TE events among those cancer patients treated with chemotherapy at adult oncology unit of TASH.

## 4. Methods

### 4.1. Study setting

The study was conducted at TASH, which is the only tertiary specialized Hospital in Ethiopia that gives service for the community in general. The Hospital located in Lideta Sub-City, Addis Ababa, Ethiopia and established in 1972 (Niguse, 2016). The Hospital has around 465 physicians, 76 pharmacists, 992 nurses and 115 other health care professionals dedicated to providing health care services. It also has around 950 administrative and support staff (College of health sciences, human resource management 2018). Besides, almost all regional and federal hospitals in Ethiopia use this Hospital as a referral unit and training site (Kebede, 2016; Woldu *et al.*, 2017).

The Ethiopian oncology service in an organized way started in TASH since 2006. This particular unit starts to work with one oncologist, one radiologist and two nurses (Tigeneh, Molla and Abreha, 2015). Above 500 adult and pediatric cases with hematologic malignancy are seen in the hematologic clinic annually. Most patients with cancer also present at the surgical, gastrointestinal (GI) and gynecology units. The most prevalent adult cancers are cervical, breast, sarcoma, head and neck and colorectal cancers. On the other hand, leukemia, lymphoma, retinoblastoma and osteosarcoma constitute the bulk of pediatric cancers (Woldeamanuel, Girma and Teklu, 2013).

### 4.2. Study design and period

An institutional-based retrospective cross-sectional study was employed and it was conducted from 1$^{st}$ March 2019 to 1$^{st}$ June 2019. The data were collected retrospectively from the medical records of patients.

### 4.3. Source and study population

#### 4.3.1. Source population

All patients who received any chemotherapy for any cancer treatment at TASH considered as source population.

### 4.3.2. Study population

Those patients who fulfill the inclusion criteria during the study period formed the study population.

## 4.4. Sampling and sample size determination

The sample size was estimated using the general formula for a single population proportion. Taking P-value of 0.5 since there is no similar study in this setup, 95% confidence interval (CI) and 1.96 for Z and 5% for d:

$$n = \frac{Z_{\frac{\alpha}{2}}^{2} P (1 - P)}{d^{2}}$$

The calculated sample size using this formula is 384. Adding 10% contingency makes the sample size 423 patients. Systematic random sampling technique was employed to recruit the study participants.

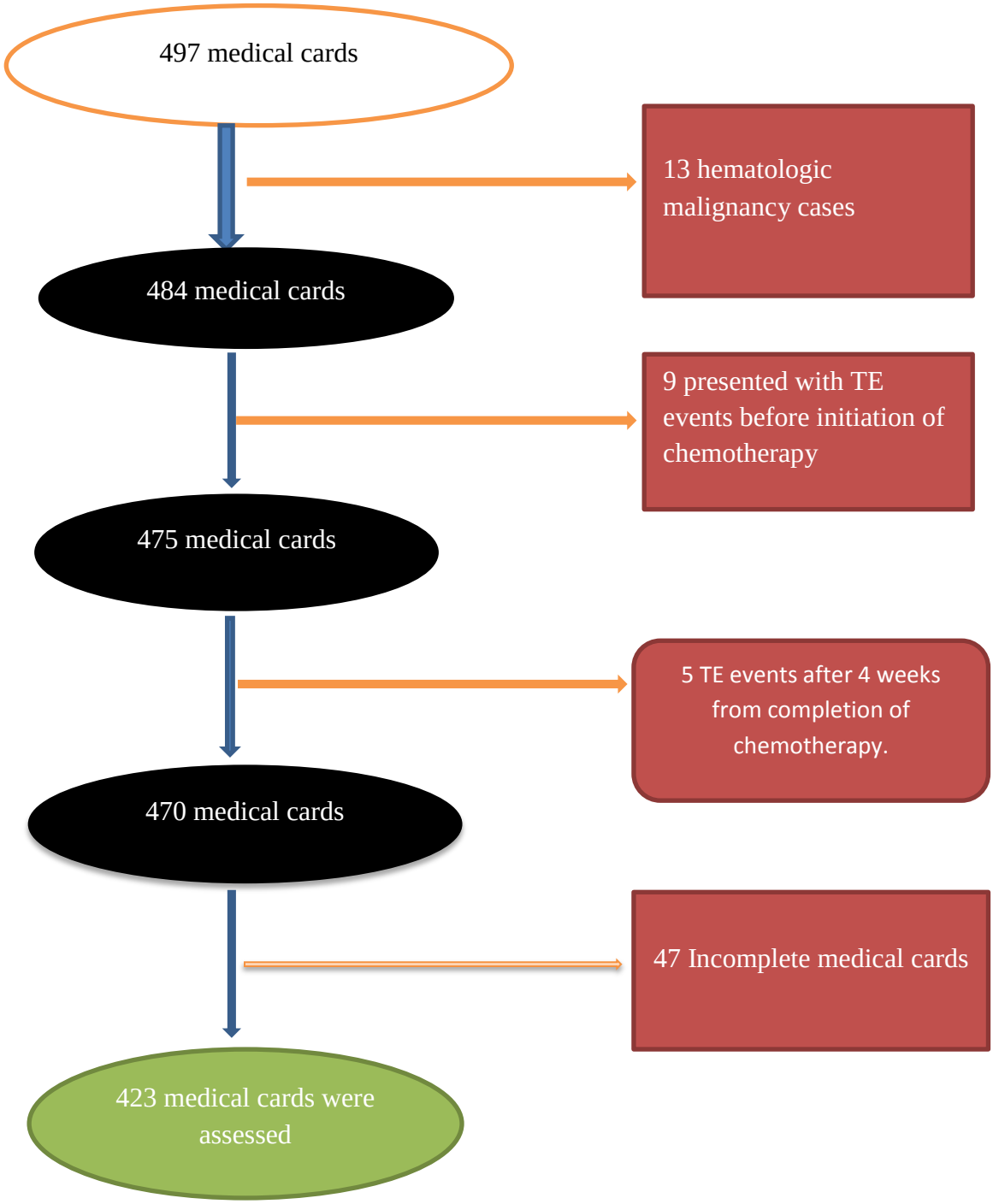


**Figure 1: Diagrammatic scheme of study participant recruitment process of patients attending in adult oncology unit of Tikur Anbessa Specialized Hospital, March 1 – June 1, 2019 (n= 423).**

The total population of patients who had been treated by chemotherapy in the past 1 year from 31 January 2018 to 31 January 2019 was 2096. Sampling interval of $K^{th}$ was obtained by dividing the total number of patients who had been treated by any chemotherapy within study period by the calculated sample size.

K= 2056/423= 5

The first patient medical record was selected randomly and then every 5 patient medical records were taken from the shelf until the required amount of sample size achieved.

### 4.5. Inclusion and exclusion criteria

#### 4.5.1. Inclusion criteria

- ✓ Patients who received chemotherapy at least for one cycle.
- ✓ Cases encountered from 31 January 2018 to 31 January 2019 at adult oncology unit of TASH.

#### 4.5.2. Exclusion criteria

- ✓ Patients with the history of prior TE events before initiation of chemotherapy.
- ✓ Patients with the diagnosis of hematologic malignancy.
- ✓ Patient's chart with incomplete records.
- ✓ Patients developed TE events after 4 weeks from the last dose of chemotherapy.

### 4.6. Study variables

#### 4.6.1. Dependent variables

- ✓ TE events after initiation of chemotherapy

#### 4.6.2. Independent variables

- **Socio-demographic variables**

- ✓ Age at initiation of chemotherapy, gender and smoking status.

- **Clinical/ medication related variables**

- ✓ Duration of chemotherapy (number of cycles), concomitant medication such as (steroids, antibiotics or GCSF), type of chemotherapy regimen containing, radiotherapy, White Blood

Cell (WBC) count, hemoglobin count, platelets count, blood transfusion, erythropoietin use for at least for 2 cycles, BMI, cancer stage and initial cancer site.

- **Patient-related variables**

✓ Pregnancy and presence of comorbid disease

### 4.7. Data collection procedure

A validated tool was employed after reviewing similar articles mainly by using "development and validation of a predictive model for chemotherapy-associated thrombosis" to collect socio-demographic characteristics, treatment-related history and history of any TE associated events after initiation of chemotherapy(Khorana *et al.,* 2016).To get comprehensive information, medication history of patients was assessed for any anticoagulant therapy before and while receiving any chemotherapeutic regimen.

The information used to calculate the Khorana risk score like WBC, hemoglobin, platelets count, BMI, cancer stage and initial cancer site were also collected from patient medical records. After that, by using Khorana risk score patients were categorized into low, intermediate and high risk. The occurrences of TE events were considered as chemotherapy-related if it happens within a month from the last dose of that particular chemotherapy. Primarily ECG and cardiac biomarkers (troponin and CK MB) were used to confirm the diagnosed MI. Chest radiographic reports were used to verify the diagnosis of PE. Doppler ultrasound was used to diagnose of DVT in TASH (Table 2).

This model helps to predict the likelihood of TE events in patients who receives chemotherapy; it uses five parameters to categorize patients into low, intermediates and high-risk groups.

**Table 2: Khorana risk assessment**

| Patients characteristics | Risk scores |
|---|---|
| Initial Site of Cancer | |
| Very High (Stomach, Pancreas) | 2 |
| High risk (Lung, Lymphoma, Gynecologic, Bladder, Testicular) | 1 |
| Pre chemotherapy platelet count 350,000/mcl or more | 1 |
| Hemoglobin level less than 10g/dl or use of red cell growth factors | 1 |
| Pre chemotherapy WBC count more than 11,000 cells/mcl | 1 |
| BMI: 35 kg/m² or more | 1 |

**Three Risk Groups:**

- Low Risk 0
- Intermediate Risk 1–2
- High Risk≥3

A total of four (two pharmacists and two nurses) were recruited as data collectors. Before the actual data collection, data collectors were trained on how to collect the necessary data from the patient's chart using the data collection instrument, and sampling techniques, the ethical principles and data management. Pre-testing was done and all necessary modifications were made on the data collection instrument.

Throughout the data collection process, close supervision was made by the principal investigator. The collected data were checked regularly for completeness and consistency.

### 4.8. Data analysis and interpretation

First, the data were checked for completeness and consistency. In order to encode, the data were initially put into Epi info version 7. Then exported to Statistical Package for Social Science (SPSS) window version 25 for analysis. Descriptive statistics were used to summarize the data while binary logistic regression analysis was used to determine factors associated with the risk of

thromboembolic events among cancer patients treated by chemotherapy. All potentially relevant variables were included in multivariable logistic regression. Finally, multivariable logistic regression was used to identify predictive factors towards TE events. *P*-value < 0.05 considered as statically significant.

### 4.9. Ethical considerations

Prior to study initiation, ethical clearance was obtained from Addis Ababa University, School of Pharmacy, ethical review board (Annex II). Also, permission was taken from the oncology department to conduct the study. Only numerical identifications were used as a reference. Confidentiality and anonymity of subject were maintained by not recording identifying details, such as names of the patients.

### 4.10. Operational definitions

**Thromboembolic events:** Include DVT, PE, which together categorized as VTE, and arterial events, including stroke and MI.

**Thromboembolic events related to chemotherapy regimens**: The occurrences of such events within the treatment period or after a month from the last dose of any chemotherapy regimen.

**Prior chemotherapy**: Patients who had been treated by any chemotherapy regimens before their current reason for admission or diagnosis.

**Prior Thromboembolic events**: Patients with the documented history of any TE disease before initiation of chemotherapy.

**Thrombo-prophylaxis**: The use anti-coagulants to prevent development of thrombosis in those patients considered at risk for developing thrombosis.

## 5. Results

### 5.1. Baseline characteristics

During the study period, 423 patient medical cards were assessed. The median age of study participants was 43 years (range: 18–83 years), the mean ± SD was 43.56 ± 14.56 and most (51.1%) were females. From the study participants, 3 (1.4%) were pregnant and 47 (11.1%) of them were smokers (Table 3).

**Table 3: Socio-demographic characteristics of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n= 423).**

| Variables | Number of Patients (%) |
|---|---|
| Age | |
| < 30 years | 79 (18.7) |
| 31 - 45 years | 139 (32.9) |
| 46 – 60 years | 127 (30.8) |
| > 60 years | 78 (18.4) |
| Sext | |
| Male | 207 (48.9) |
| Female | 216 (51.1) |
| Pregnancy | |
| Pregnant | 3 (1.38) |
| Not pregnant | 213 (98.61) |
| Smoking habit | |
| Smoker | 47 (11.1) |
| Non-smoker | 318 (75.2) |
| Unknown | 58 (13.7) |

### 5.2. Clinical characteristics

In most of the study participants the primary site of cancer was breast 119 (28.1%), followed by GI 113 (26.7%) and head and neck 63 (14.9%). At time of the initiation of chemotherapy, most of the study participants had performance status of 1 and 2 (50.1% and 35.9), respectively. Nearly half of the study participants 204 (48.2%) had stage 4 diseases at a time of chemotherapy

initiation. More than 1/3$^{rd}$ of the study participants had unknown or undocumented history about their comorbid diseases. Retroviral Infections were recorded on a significant number of participants 27 (6.4%), followed by hypertension 18 (4.3%) and type 2 *Diabetes mellitus* 13 (3.1%) (Table 4).

**Table 4: Clinical characteristics of patients attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n=423).**

| Variables | Number of patients (%) |
|---|---|
| BMI | |
| below 24.9 | 281 (66.4) |
| 25.0-29.9 | 127 (30.0) |
| 30.0-34.9 | 13 (3.1) |
| above 35.0 | 2 (0.5) |
| Performance status | |
| ECOG 0 | 10 (2.4) |
| ECOG 1 | 212 (50.1) |
| ECOG 2 | 152 (35.9) |
| ECOG 3 | 45 (10.6) |
| ECOG 4 | 3 (0.7) |
| Unknown | 1 (0.2) |
| Primary site of cancer | |
| Breast | 119 (28.1) |
| Lung | 16 (3.8) |
| Gynecological | 47 (11.1) |
| Head and Neck | 63 (14.9) |
| Gastrointestinal | 113 (26.7) |
| Others | 65 (15.4) |
| Cancer stage | |
| Stage 0-2 | 28 (6.6) |
| Stage 3 | 173 (40.9) |
| Stage 4 | 204 (48.2) |
| Unknown | 18 (4.3) |

| | |
|---|---|
| Comorbidity | |
| HIV/AIDS | 27 (6.4) |
| Hypertension | 18 (4.3) |
| *Type 2 Diabetes* | 13 (3.1) |
| Chronic Kidney Disease | 12 (2.8) |
| Congestive Heart Failure | 10 (2.4) |
| Anemia | 10 (2.4) |
| Peptic Ulcer Disease | 7 (1.7) |
| Hypertension + Type 2 Diabetes | 6 (1.4) |
| Asthma | 4 (0.9) |
| Pulmonary Tuberculosis | 3 (0.7) |
| Disseminated Tuberculosis | 2 (0.5) |
| Congestive Heart Failure + Hypertension | 2 (0.5) |
| HIV/AIDS + Hypertension | 2 (0.5) |
| Unknown | 297 (70.2) |
| Others* | 10 (2.4) |

**Each patient had either one of the following (HIV/AIDS + asthma, Benign Prostate Hyperplasia, asthma + type 2 diabetes, congestive heart failure + anemia, rheumatoid arthritis, retroviral Infection + hypertension + anemia, HIV/AIDS + congestive heart failure, schizophrenia, type 1 diabetes + hypertension or Peripheral arterial disease + type 2 diabetes.*

Regarding, the Khorana risk score, more than half 235 (55.6%) of them were categorized as intermediate risk (Figure 2).

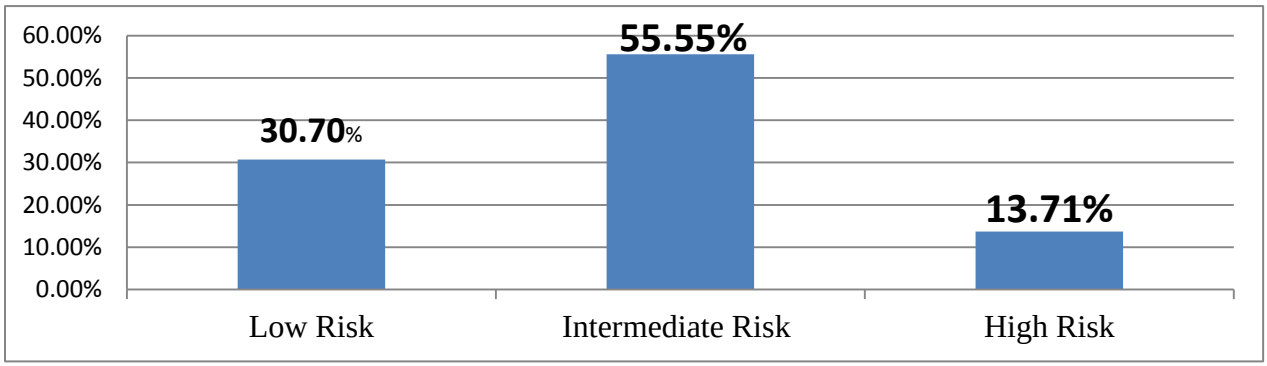


**Figure 2: Khorana risk score of study participants of patients attending in adult oncology unit of TASH, Addis Ababa, Ethiopia, from January 2018- January 2019**

### 5.3. Treatment modalities

Almost in all study participants 414 (97.9 %) steroid was incorporated in the treatment regimen. A significant number of study participants 176 (41.6 %) were treated using the combination of chemotherapy and radiation. Almost half 208 (49.2 %) of the study subjects received 4-6 cycle of chemotherapy. Only 2 (0.5 %) patients have received erythropoietin (EPO) at least for two cycles in their treatment course. Prophylactic myeloid growth factor was used in 120 (28.4 %) of patients and 78 patients (20.6 %) got blood transfusion. Majority of the study participants, 360 (85.1 %) were new for chemotherapy (Table 5).

**Table 5: Treatment characteristics of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n= 423).**

| Treatment Modalities | Number of Patients (%) |
|---|---|
| Chemotherapy + Surgery within last month | 65 (15.4) |
| Chemotherapy + Radiation therapy | 176 (41.6) |
| Chemotherapy cycles | |
| Below 3 cycles | 110 (26.0) |
| Between 4-6 cycles | 208 (49.2) |
| Above seven cycles | 105 (24.2) |
| Use of erythropoietin at least for two-cycle | |
| Yes | 2 (0.5) |
| No | 421 (99.5) |
| Prophylactic myeloid growth factor use | |
| Yes | 120 (28.4) |
| No | 303 (71.6) |
| Steroid use | |
| Yes | 414 (97.9) |
| No | 9 (2.1) |
| Blood transfusion | |
| Yes | 87 (20.6) |
| No | 336 (79.4) |
| Type of treatment | |
| New | 360 (85.1) |
| Relapse or recurrence | 63 (14.9) |

### 5.4. Chemotherapy regimen

A wide range of chemotherapy combinations were used since the study incorporated patients with a variety type of cancer. From these, 79(18.7%) of patients were on doxorubicin, Cyclophosphamide and Paclitaxel and 62 (14.7%) patients were treated by a combination of Cisplatin and 5-FU (Table 6).

**Table 6: Type of chemotherapy regimen of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018 - January 2019, (n= 423).**

| Specific chemotherapy regimen | Number of patients (%) |
|---|---|
| Doxorubicin + Cyclophosphamide + Paclitaxel | 79 (18.7) |
| Cisplatin + 5-FU | 62 (14.7) |
| Cisplatin + Paclitaxel | 48 (11.3) |
| Doxorubicin + Cyclophosphamide | 35 (8.3) |
| Vincristine + Doxorubicin + Cyclophosphamide | 29 (6.9) |
| 5-FU + Folinic acid + Oxaliplatin | 21 (5) |
| Cisplatin + Doxorubicin | 16 (3.8) |
| Carboplatin + Paclitaxel | 15 (3.5) |
| Doxorubicin + Dacarbazine | 11 (2.6) |
| Capecitabine + Oxaliplatin | 11 (2.6) |
| Cisplatin + Gemcitabine | 11 (2.6) |
| Cisplatin + 5-FU for 2 cycle Cisplatin + Paclitaxel for 4 cycles. | 10 (2.36) |
| Cisplatin | 6 (1.4) |
| Folinic acid + 5-FU + Irinotecan | 5 (1.2) |
| Cisplatin + Etoposide | 5 (1.2) |
| Cisplatin + Etoposide + Bleomycine | 5 (1.2) |
| 5-FU + Folinic acid + Oxaliplatin (FOLFOX )for 3 cycles + 5-FU + Folinic acid + Irinotecan (FOLFORI) for 3 cycles | 4 (1.0) |
| Cisplatin + 5-FU for 6 cycle + Carboplatin + Paclitaxel for 2 cycles. | 4 (1.0) |
| FOLFOX for 5 cycle + Capecitabine for 3 cycle | 3 (0.7) |
| Carboplatin + 5-FU | 3 (0.7) |
| Carboplatin + Etoposide | 2 (0.5) |
| Cisplatin + Doxorubicin + Cyclophosphamide | 2 (0.5) |
| FOLFORI for 2 cycle + Capecitabine + Oxaliplatin for 6 cycle | 2 (0.5) |
| Paclitaxel | 2 (0.5) |
| Others * | 29 (6.85) |

**Each patients were received either one of the following; doxorubicin + cyclophosphamide for 4 cycles followed by docetaxel 3 cycles, doxorubicin + cyclophosphamide for 4 cycles then gemcitabine for 6 cycles, etoposide, doxorubicin + cyclophosphamide + 5-FU, dacarbazine, doxorubicin + cyclophosphamide + paclitaxel for 8 cycles followed by carboplatin + paclitaxel for 6 cycles, doxorubicin + 5-FU, baclutamide, carboplatin + 5-FU, epirubicin + Cisplatin +5-FU, FOLFOX for 2 cycles followed by Capecitabine + oxaliplatin for 3 cycles, FOLFOX for 2 cycles then bevacizumab, G, cisplatin + doxorubicin + vinblastine + methotrexate, cisplatin + doxorubicin + etoposide, cisplatin + doxorubicin + paclitaxel, cisplatin + 5-FU + doxorubicin, cisplatin + bleomycine + epirubicin, cisplatin +5-FU for 6 cycles + cisplatin + paclitaxel for 6 cycles, cisplatin + paclitaxel for 3 cycles followed by capecitabine for 4 cycles, cisplatin + paclitaxel for 4 cycles + carboplatin + paclitaxel for 6 cycles, cisplatin + paclitaxel for 4 cycles + vinorelbine + gemcitabine for 5 cycles, temozolomide or capecitabine.*

### 5.5. Hormonal therapy

Among the study participants around 1/4$^{th}$ of them used hormonal therapy and tamoxifen was the most frequently used 60 (60%) followed by Anastrozole 37 (37 %) (Figure 3). During the study period patients treatment was shifted from one hormonal agent to another because of stock out of medications, this was frequently happened particularly in patients with breast cancer.

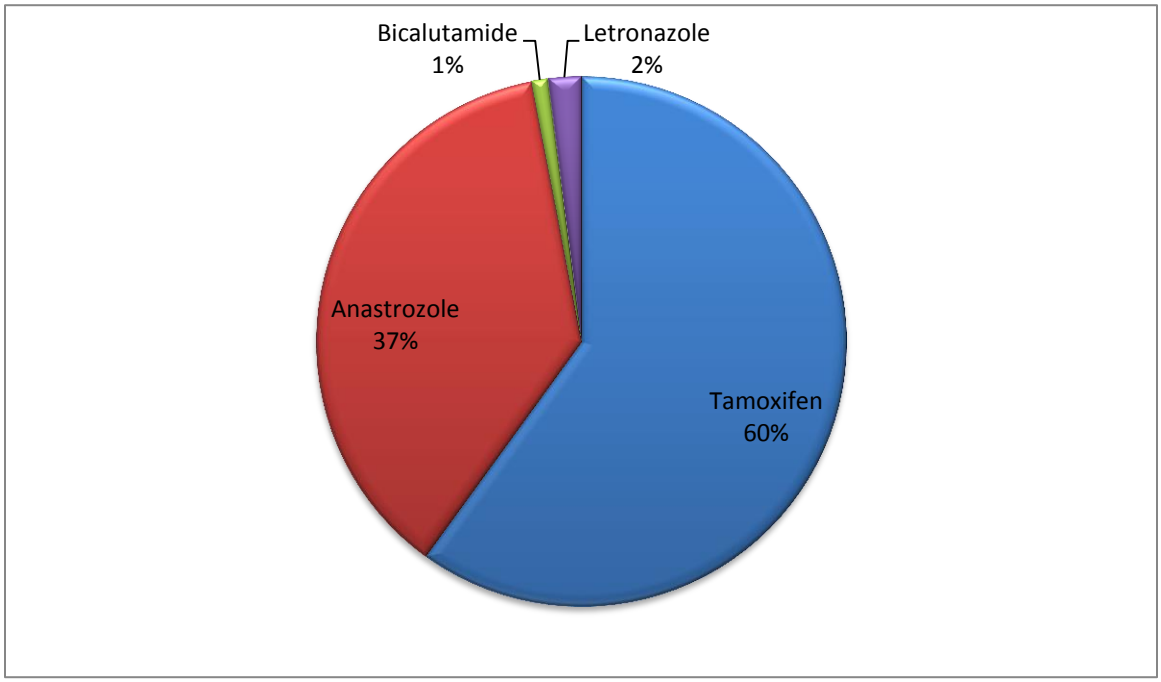


**Figure 3:** Types of hormonal treatment of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, January 2018 - January 2019, (n=423).

### 5.6. Incidence of thromboembolic events

Among study participants, TE events encountered in 43 (10.2 %) of them and DVT accounted the highest proportion36 (85.7 %) (Figure 4). Regarding the site, chronic portal and splenic vein

thrombosis, left upper and lower thigh acute DVTs, sagittal sinus thrombosis, azygos vein thrombosis with collaterals, bilateral proximal and distal lower leg extremity acute DVTs, bilateral lower limb acute DVTs, both right and left lower leg extremity DVTs, left atrial thrombosis and both right and left distal upper arm extremity DVTs were among the most frequent ones.

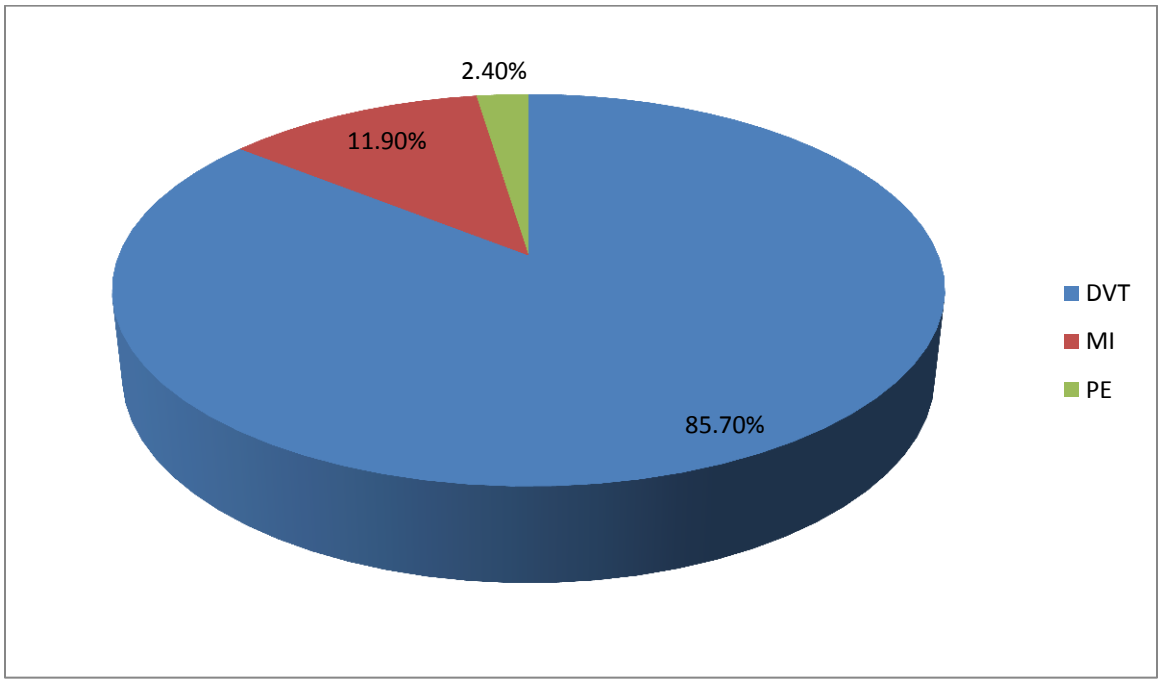


**Figure 4: Incidence of thromboembolic events of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n= 423).**

We studied the effect of the combination of chemotherapy-related with TE events. The rate was highest in (FOLFOX), (Cisplatin + paclitaxel), and (*doxorubicin* + cyclophosphamide + paclitaxel) which accounted similar proportion, which were 6 (13.95%) TE events from each regimen. The rate of TE events were 4 (9.3%) in patients who received (FOLFORI) (Table 7).

**Table 7: Thromboembolic events with respect to chemotherapies of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n= 423).**

| Chemotherapy regimens | Number of TE events (%) | Number of DVTs | Number of MIs | Number of PEs |
|---|---|---|---|---|
| FOLFOX | 6 (13.95) | 6 | 0 | 0 |
| Cisplatin + Paclitaxel | 6 (13.95) | 2 | 3 | 1 |
| doxorubicin + Cyclophosphamide + Paclitaxel | 6 (13.95) | 4 | 2 | 0 |
| FOLFORI | 4 (9.3) | 4 | 0 | 0 |
| Cisplatin + doxorubicin | 3 (6.97) | 3 | 0 | 0 |
| Cisplatin + 5-FU | 2 (4.65) | 2 | 0 | 0 |
| Vincristine + doxorubicin + Cyclophosphamide | 2 (4.65) | 2 | 0 | 0 |
| Cisplatin + Gemcitabine | 2 (4.65) | 2 | 0 | 0 |
| Carboplatin + Paclitaxel | 2 (4.65) | 2 | 0 | 0 |
| Capecitabine +Oxaliplatin | 2 (4.65) | 2 | 0 | 0 |
| Cyclophosphamide + doxorubicin + Cisplatin | 2 (4.65) | 2 | 0 | 0 |
| Others * | 4 (9.3) | 4 | 0 | 0 |

**Each DVT occurred in patients received either one of the following chemotherapy regimens; Cisplatin + etoposide + doxorubicin, doxorubicin + cyclophosphamide + vincristine + prednisolone, doxorubicin + cyclophosphamide or methotrexate + vinblastine + cisplatin + doxorubicin.*

### 5.7. Predictive factors associated with thromboembolic events.

Of the included variables in multivariable logistic regression, only blood transfusion, a primary site of cancer with GI malignancy and performance status showed statically significant association. The odds of TE events in patients who did not undergo blood transfusion at a time of chemotherapy administration were reduced by 63 %, compared to their counterparts (AOR= 0.37, 95 % CI: 0.16-0.89, P= 0.026).

On the other hand, primary site of cancer has shown statically significant association with the outcome variable. Patients with GI cancer had 10.64 times increased odds of developing TE events compared to breast cancer, (AOR= 10.64, 95 % CI: 1.083-10.4573, P= 0.043).

In addition, ECOG performance score showed a significant association with TE events in which patients with ECOG score of 2 and 3-4, (AOR= 38.11, 95 % CI: 7.60-19.090, P= 0.000) and (AOR= 2.71, 95 % CI: 1.12-6.54, P = 0.026) respectively had increased risk of developing TE events as compared to patients with ECOG score of 0-1 (Table 8).

**Table 8: Predictive factors associated with thromboembolic events of study participants attending in adult oncology unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2018- January 2019, (n= 423).**

| Variables | TE events, n (%) | | Crude OR (CI 95%) | Adjusted OR (CI 95%) |
|---|---|---|---|---|
| Prior Chemotherapy | | | | |
| Yes | 7 (17.5) | 33 (82.5) | 1.00 | |
| No | 36 (9.39) | 347 (90.6) | 0.489 (0.202-1.185) | 0.573 (0.18-1.823) |
| Blood Transfusion | | | | |
| Yes | 22 (25.28) | 65 (74.71) | 1.00 | |
| No | 21 (6.25) | 315 (93.75) | 0.197 (0.12-0.379) | 0.379 (0.161-0.891)* |
| Primary site | | | | |
| Breast | 6 (5.04) | 113 (94.95) | 1.00 | |
| Lung | 1 (6.25) | 15 (93.75) | 3.836 (1.348-10.922) | 12.936 (0.634-263.9) |
| Gynecological | 6 (12.76) | 15 (93.75) | 3.056 (0.365-25.598) | 5.036 (0.447-56.754) |
| Head and neck | 1 (1.58) | 62 (98.41) | 1.392 (0.475-4.075) | 2.924 (0.656-13.036) |
| GI | 18 (15.92) | 95 (84.07) | 12.63 (1.579-10.1030) | 10.641 (1.083-10.4573)* |
| Other | 11 (16.92) | 54 (83.07) | 1.075 (0.473-2.44) | 1.54 (0.479-4.952) |
| Performance Status | | | | |
| EGOG 0-1 | 2 (0.9) | 220 (99.09) | 1.00 | |
| ECOG 2 | 23 (15.13) | 129 (84.86) | 63.87 (14.131-28.8689) | 38.112 (7.609-19.0902)* |
| ECOG 3-4 | 18 (36.73) | 31 (63.26) | 3.257 (1.568-6.764) | 2.713 (1.124-6.549)* |
| Khorana risk score | | | | |
| Low | 6 (4.61) | 124 (95.38) | 1.00 | |
| Intermediate | 26 (11.06) | 209 (88.93) | 4.837 (1.69-13.82) | 1.638 (0.399-6.719) |
| High | 11 (18.96) | 47 (81.03) | 1.881 (0.869-4.074) | 0.901 (0.303-2.686) |
| Erythropoietin use | | | | |
| Yes | 1 (50.00) | 1 (50.00) | 1.00 | |
| No | 42 (9.97) | 379 (90.02) | 0.11 (0.007-1.804) | 0.996 (0.45-22.087) |

| | | | | |
|---|---|---|---|---|
| Myeloid Growth Factor | | | | |
| Yes | 16 (13.33) | 104 (86.66) | 1.00 | |
| No | 27 (8.91) | 276 (91.08) | 0.636 (0.329-1.228) | 0.793 (0.339-1.854) |
| Antibiotics | | | | |
| Yes | 31 (12.3) | 221 (87.7) | 1.00 | |
| No | 12 (7.01) | 159 (92.98) | 0.538 (0.268-1.080) | 0.461 (0.195-1.092) |
| Fluorinated Pyrimidine | | | | |
| Yes | 18 (13.23) | 118 (86.76) | 1.00 | |
| No | 25 (8.71) | 262 (91.28) | 0.626 (0.329-1.191) | 0.85 (0.326-2.214) |
| Platinum Analogs | | | | |
| Yes | 30 (12.24) | 215 (87.75) | 1.00 | |
| No | 13 (7.30) | 165 (92.69) | 0.565 (0.286-1.116) | 0.956 (0.321-2.93) |

**Variables which showed significant association with the occurrences of TE events.*

## 6. Discussion

To our knowledge this retrospective cross-sectional study is the first of its kind in Ethiopia which gives insight into TE events among cancer patients treated with chemotherapy at adult oncology unit of TASH and aimed to identify predictive factors associated with TE events among those patients with cancer treated with chemotherapy.

Four weeks of follow up for the development of TE events in patients receiving chemotherapy was chosen in this study based on previous related literature data (Moore *et al.*, 2011; Zahir *et al.*, 2017). Moreover, it seems a reasonable follow-up period for capturing most, if not all, events occurring as a result of the drug intervention.

In this study, medical records of 423 patients treated using different chemotherapies for a variety of cancer types were assessed. It was observed that there was a high incidence of TE events (10.2 %) during the period of administration or within four weeks of completion of treatment. It was believed that the true incidence may even be higher as the study might have failed to detect every patient with TE events because of its retrospective nature.

However, the finding (incidence of TE) was similar to studies done in different parts of the world: Pakistan 10.5 % (Zahir *et al.*, 2017), University of Michigan (USA) 11.6 % (Greco *et al.*, 2017), 12.5 % both in Chicago (USA) and United Kingdom (Pant *et al.*, 2014; Papaxoinis *et al.*, 2018) and 13.8 % McMaster University (a multi-institutional rétrospective analysis) (Duivenvoorden *et al.*, 2016). On the contrary some other studies have reported a higher rate of TE events among cancer patients treated with chemotherapy. For example a study done in the United Kingdom has found 21 % of TE events (Maraveyas *et al.*, 2011). The reason for this higher incidence rate could be an increased detection of TE events with improved imaging modalities, inclusion of, patients with asymptomatic TE events and the diagnosis of arterial events. Moreover, the study was conducted on pancreatic cancer patients and patients with GI malignancy only which by itself is thought to increases the risk of TE events.

Lower TE incidence was reported in the Jordan study (6.6 %) (Abdel-razeq *et al.*, 2018) and study conducted in Italy (6.6%) (Reni *et al.*, 2007). Most of the study participants in the Jordan study were classified as lower risk for TE and this could be the explanation for lower rate of TE

events. In addition, the variation could be due to difference in the study design and setting as well as venous thrombosis, arterial thrombosis was not well-described in these studies.

In the current study, about 85.7 % of TE events were found to be DVT. The finding of this study was in line with several studies done elsewhere, which ranges from 74-87.2 %, (Piotr, Malcolm and Ian, 1998; Maraveyas *et al.*, 2011; Abdel-razeq *et al.*, 2018). But higher than that of a study conducted in United Kingdom (17.56 %) (Papaxoinis *et al.*, 2018), Australia (63.6 %) (Blom *et al.*, 2006), and USA (6.3 %) (Pant *et al.*, 2014). The lower rate of TE events in the above studies could be due a significant number of study participants grouped into the low-risk category for Khorana risk score. Moreover, the variation might be in some of the studies treatment with chemotherapy was not one of the inclusion criteria which means they incorporate patients who are not treated by chemotherapy, which thought as one of the risk factors for TE.

In the present study, PE encountered in 2.4 % of TE events, and this was comparable with a study conducted in the USA(7 %) (Pant *et al.*, 2014). However, almost in all other studies, the finding of PE was significantly higher than ours. A study from Pakistan found that PE accounted for 21.4 % TE (Zahir *et al.*, 2017), a study done in the United Kingdom (21.62 %) (Maraveyas *et al.*, 2011), a study from Jordan showed that PE rate was 26 % (Abdel-Razeq *et al.*, 2011) and a multicenter study reported a 33.3 % (Duivenvoorden *et al.*, 2016). These variations might be due to in our institution's there is a weak record-keeping system and higher mortality rate before the detection or diagnosis of PE. Moreover there are other reasons for higher PE incidence rates, in some of the studies patients had prolonged hospitalization and multiple risk factors for TE (BMI $\geq 25$, smoking history, comorbid disease like sepsis, congestive heart failure, Diabetic Mellitus, chronic obstructive pulmonary disease, surgery in the past 3 months, patients with metastasis disease and previous VTE) these could contribute for a higher rate of PE. Another explanation for such varied result may be in the above studies, they used extended study period. Furthermore, their great diagnostic techniques help them to diagnose PE and in some of the studies, the study design by itself favors for identification of the events.

The incidence of MI was 11.9 % which is almost similar to the Jordan study (12.7 %) (Abdel-razeq *et al.*, 2018). However, it was higher than a study conducted in USA which ranged from 8.2% to 9.4% (Moore *et al.*, 2011; Papaxoinis *et al.*, 2018). In contrary relatively higher

incidences were reported in a study done in Canada (20.0 % ) (Piotr, Malcolm and Ian, 1998). This difference might be in the Canadian study 70 % of TE events occurred at a time of 6 coldest months of the year this means the weather by itself could be confounding factor. Also, compare to ours, most of the study participants were at an advanced age, and they received a longer duration of a chemotherapy course. On the other hand lower rates of MI incidence were reported United Kingdom (2.7 %) (Maraveyas *et al.*, 2011) and in another multi-centered study (6.96 %) (Duivenvoorden *et al.*, 2016). The discrepancy might be explained by in case of our study due to the retrospective nature, we cannot sort out other confounding factors which can be responsible for MI.

Moreover, in some studies, combined TE events on a single patient had been seen. A study from Jordan reported around 5.8 % of TE events were PE plus DVT (Abdel-Razeq *et al.*, 2017). In another study, there was 2.6 % combined arterial thrombosis with DVT had been noticed (Abdel-razeq *et al.*, 2018). Unlike these, no combined TE event has been documented in this study which may be due to inadequate documentation and record-keeping system.

Identifying predictors of TE events in patients who have been treated by chemotherapy is crucial. It helps to identify and prevent patients who are liable for such events and increase practitioner concern regarding TE. Since TE events associated with significant mortality and morbidity rate helps to consider thrombo-prophylaxis in high-risk patients.

Similar to some other studies (Bright *et al.*, 2016; Zahir *et al.*, 2017; Abdel-razeq *et al.*, 2018); history of blood transfusion while chemotherapy, the primary site of the tumor with GI malignancy and performance status showed a statistically significant association with the development of TE events. In this study the odds of TE events in patients who do not undergo blood transfusion at a time of chemotherapy administration were reduced by 63 %, patients with gastrointestinal cancer had 10.64 times increased odds developing TE events compared to breast cancer and ECOG performance score showed a significant association with TE events in which patients with ECOG score of 2 and 3-4, had increased risk of developing TE events as compared to patients with ECOG score of 0-1.

Advanced cancer stage (metastasis disease), chemotherapy, Khorana risk score, age, overweight or obesity and CVC (Piotr, Malcolm and Ian, 1998; Blom *et al.*, 2006; Moore *et al.*, 2011;

Papaxoinis *et al.*, 2018), often thought to be predictors of VTE risk, were not found to play a role in our study. In previous studies reports found that no association of age, sex, race, performance status, staging, Khorana risk score, chemotherapy, BMI, CVC, radiotherapy and surgery were with the occurrence of TE events (Pant *et al.*, 2014; Duivenvoorden *et al.*, 2016; Zahir *et al.*, 2017; Abdel-razeq *et al.*, 2018). The discrepancy might arise from their study designs and study participants with different risk level for TE.

In recent literature, a specific group of chemotherapies such as platinum analogs and fluorinated pyrimidine's showed a significant association with the occurrences of TE (Zahir *et al.*, 2017; Abdel-razeq *et al.*, 2018). Hence an attempt has been made whether there is such an association present in our study. In doing so, we classify chemotherapy regimens into platinum's and fluorinated pyrimidine's analogs; however, we found no association with the outcome variable. The justifiable reason for this could be in the Jordan study all of their study participants were exclusively from cisplatin based regimens and in Pakistan study their study design (cohort) favors in order to explore this kinds of association.

## 7. Limitations of the study

- ✓ Due to the retrospective nature of the study, there is still a chance that we might have missed some patients with TE.
- ✓ The study conducted on a single-center; hence generalization to other patients treated for cancer in other recently opened centers may not be possible.
- ✓ The disease characteristics by itself might have expose this particular group of patient to TE events compare to the general population.
- ✓ The hospital record keeping system was poor.

## 8. Conclusion

The incidence of TE events among cancer patients who had been treated by chemotherapy was high compared to other studies. The most familiar TE event was DVT. Performance status, blood transfusion, and the primary site of the tumor with GI malignancy were significantly associated with the occurrence of TE events.

## 9. Recommendation

Based on the study findings, the following recommendations were made:

- ✓ The Khorana risk assessment tool needs to be implemented by clinicians for ambulatory patients who plan to receive chemotherapy to stratify TE risk.
- ✓ For selected high risk patients thrombo-prophylaxis needed to be considered.
- ✓ Organize educational sections to health care providers to create awareness on TE events associated with cancer and its treatment.
- ✓ In addition to thrombo-prophylaxis non-pharmacological intervention such as compression stockings needs to be considered.
- ✓ The hospital record-keeping problems should be improved.

## 10. References


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## 11. Annex

### 11.1. Annex I: Data abstraction format

**STUDY CHECKLIST**

**Sociodemographic Data:**

1. Age: ----------
2. Sex: a. Male b. Female
3. If it is females: a. Pregnant b. Not pregnant
4. Smoking habit a. Yes b. No c. Unknown

**Chemotherapy and cancer-related data**

1. Any history of prior thromboembolism (before chemotherapy)
   a. Yes b. No
2. Prior chemotherapy history
   a. Yes b. No
3. Type of treatment
   a. New b. Relapse/recurrence
4. Any thromboembolic events after initiation of chemotherapy
   a. Yes b. No
5. If yes, what type of thromboembolic events is that
   a. Deep vein thrombosis c. MI, E. Combination of the above
   b. Pulmonary embolism d. Other Arterial events F. None
6. Performance status, ECOG
   a. 0 b. 1 c.2 d. 3 e. 4 f. 5 g. unknown
7. Blood transfusion during chemotherapy
   a. Yes b. No
8. The primary site of cancer
   a. Breast b. Lung c. Gynecologic d. Head and neck e. Gastrointestinal
   f. Other site
9. Diagnosis ----------
10. Cancer stage
    a. 0-2 b. 3 c. 4 d. Unknown

11. Comorbidities----------

12. BMI

a. Below 24.9 b. 25.0-29.9 c. 30.0-34.9 d. above 35.0

13. Surgery within the last one month

a. Yes b. NO

14. Treatment incorporates both radiation and chemotherapy

a. Yes b. No

**Baseline laboratory values**

| | Yes | No |
|---|---|---|
| Hemoglobin level less than 10g/dl | | |
| WBC count more than 11,000 cells/mcl | | |
| Platelet count 350,000/mcl or more | | |

15. Khorana Risk Score

a. Low = risk 0 b. Intermediate= risk 1-2 c. High= risk greater or equal to 3

**Other medications**

16. Erythropoietin stimulating agents reported up to 2 cycles a. Yes b. No

17. Prophylactic myeloid growth factors a. Yes b. No

18. Documented antibiotics within the last 3 month a. Yes b. No

19. Corticosteroids a. Yes b. No

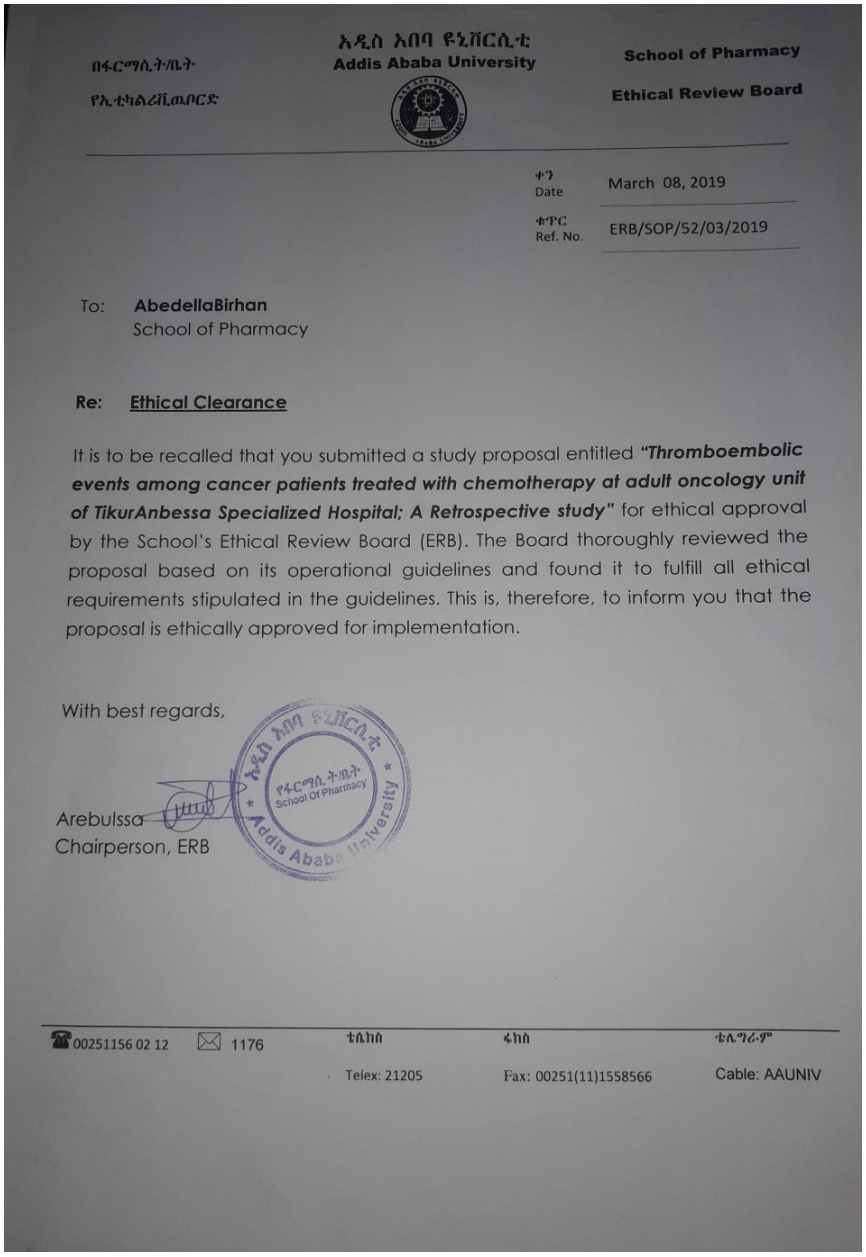
**Chemotherapy combinations used and number of cycles**

20. ----------

**Hormonal therapy**

| | | | |
|---|---|---|---|
| Tamoxifen | | Finasteride | |
| Anastrozole | | Letronazole | |
| Bicalutamide | | Others | |

## 11.2. Annex II: Ethical clearance



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Addis Ababa University

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School of Pharmacy
Ethical Review Board

ቀን Date: March 08, 2019

ቁጥር Ref. No.: ERB/SOP/52/03/2019

To: **AbedellaBirhan**
School of Pharmacy

**Re:** **Ethical Clearance**

It is to be recalled that you submitted a study proposal entitled ***"Thromboembolic events among cancer patients treated with chemotherapy at adult oncology unit of TikurAnbessa Specialized Hospital; A Retrospective study"*** for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Arebulssa
Chairperson, ERB

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