Incidence and Determinants of Chemotherapy Associated Thromboembolic Events among Ethiopian Patients Treated for Solid Malignancy: A Retrospective Cross-Sectional Study

Abdella Birhan Yabeyu1, Shemsu Umer Hussen, BPharm, MSc, PhD2, Wondemagegnhu Tigneh, MD3, and Atalay Mulu Fentie, BPharm, MPharm2

Abstract
Venous thromboembolism is a common problem in patients treated for cancer, although the reported incidence varies widely between studies. This was the first study in its kind in Ethiopia and aimed to assess the incidence and determinants of chemotherapy associated thromboembolic events among patients treated for solid malignancy. An institution-based retrospective cross-sectional study was conducted from 1st March to 1st June, 2019 at adult oncology center of Tikur Anbessa Specialized Hospital. Systematic random sampling technique was employed to recruit 423 study participants. Patients who have received at least a single cycle of any chemotherapy regimen were included in the study. Khorana risk assessment tool was used to predict chemotherapy associated thrombosis. Descriptive statistics were used to summarize the data while multivariable logistic regression was employed to explore associations among variables of interest. 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%). In multivariable logistic regression, blood transfusion, a primary site of cancer with gastrointestinal malignancy and performance status showed statistically significant association towards the occurrences of thromboembolic events. The incidence of chemotherapy associated thromboembolic events among patients treated for solid malignancy was comparable to other studies. Hence, other prospective randomized trials are needed to see the importance of thrombo-prophylaxis in such high-risk patients.

Keywords
chemotherapy, Ethiopia, solid malignancy, thromboembolic events

Date received: 15 December 2021; revised: 2 February 2022; accepted: 15 March 2022.

Introduction
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. 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. Currently, treatment modality for cancer incorporates surgery, systemic therapies and radiotherapy. They can be given alone or in combination, either with the curative or palliative purpose. However, in addition to other risk factors, most cancer treatment options have been shown to increase the risk of venous thromboembolism (VTE) despite the reported incidence (ranged from 6.6% to 21%) varies widely between studies. Other risk factors include prolonged hospitalization, central venous catheters (CVC), type of malignancy, cancer stage and supportive therapies

1 Department of Pharmacy, College of Medicine and Health Sciences, Ambo University, Ambo, Ethiopia
2 Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
3 Department of Oncology, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Corresponding Author:
Shemsu Umer Hussen, Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

Email: nasifshemsu@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
such as blood transfusion. The VTE events can be classified into deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial events, like stroke and myocardial infarction (MI). These events are significant contributors to morbidity and mortality in these particular patients.

Multiple risk factors have been identified for chemotherapy associated VTE in patients treated for solid malignancy. The risk factors are categorized either as patient characteristics or malignancy-related characteristics, including specific therapeutic intervention. Patients treated with chemotherapy have several-fold higher risk of developing VTE compared with the general population, with relative risks ranging from 4 to 7. The estimated annual incidence of VTE in these group of patients is 0.5%, and it is one of the leading cause of death.

Several studies implicated, genetics difference is also one of the contributing factors for the occurrence of VTE. If it is possible to anticipate the occurrences of chemotherapy associated VTE, it would be rational to develop strategies to tackling possible events. Besides, knowing the incidence and associated factors are important to reduce mortality, morbidity, hospitalization, treatment costs and also to improve patient’s quality of life.

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 for solid malignancy at the oncology unit of Tikur Anbessa Specialized Hospital (TASH). Therefore, this study was aimed to assess the incidences and determinants of chemotherapy associated VTE among patients treated for solid malignancy at the oncology unit of TASH, Addis Ababa, Ethiopia.

Material and Methods

Study Setting

The study was conducted at TASH, which is the only tertiary specialized Hospital in Ethiopia that gives comprehensive cancer care in Ethiopia. The Hospital has around 465 physicians, 76 pharmacists, 992 nurses and 115 other health care professionals dedicated in providing health care services. It also has around 950 administrative and support staff (College of Health Sciences, human resource management 2018).

The Hospital has about 700 beds and serves more than 500,000 patients per year in its 20 outpatient specialty clinics, inpatient and emergency departments. The Ethiopian cancer treatment was started in TASH in the organized way since 2006. Overall, adult oncology center serves more than 850 patients per month and around 10,000 patients per year. Specialized comprehensive and clinical services, which are not available in other public or private institutions, are offered to the whole nation by this hospital. The most prevalent adult cancers are cervical, breast, sarcoma, head and neck and colorectal cancers.

Study Design and Period

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

Source and Study Population

All patients who received any chemotherapy for any solid malignancy at TASH were considered as source population. Those patients who fulfill the inclusion criteria during the study period formed the study population.

Inclusion and Exclusion Criteria

Patients who received at least one cycle of chemotherapy were included in the study. Patients with history of prior TE events before initiation of chemotherapy, patients with the diagnosis of non-solid malignancies, patient’s chart with incomplete records and patients developed VTE after 4 weeks from the last dose of chemotherapy were excluded from the study.

Sampling and Sample Size Determination

Single population proportion formula was used to calculate sample size with assumption that overall prevalence of satisfied patients is 50% with a margin of error 5% and confidence level of 95% and detection power of 80%. Based on the power calculation and sample size needed to demonstrate incidence of VTE after adding a 10% contingency, a total of 423 study participants were recruited for the study. The 50% prevalence was chosen due to lack of published similar studies conducted in Ethiopia. Systematic random sampling technique was employed to recruit the study participants.

The total population of patients who had been taking chemotherapy in the past one year from 31 January 2018 to 31 January 2019 was 2096. Sampling interval of K was obtained by dividing the total number of patients who had been treated by any chemotherapy within study period by the calculated sample size (Figure 1).

Data Collection Instruments and Techniques

A validated tool was employed after reviewing similar articles mainly “development and validation of a predictive model for chemotherapy-associated thrombosis” to collect socio-demographic characteristics, treatment-related history and history of any VTE associated events. 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 VTE 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 diagnosis of MI. Chest radiographic reports were used to verify the diagnosis of PE. Doppler ultrasound was used to diagnose DVT.
Data Collectors Recruitment and Training
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, sampling techniques, the ethical principles and data management. Pilot-testing was done on 41 patients and then all necessary modifications were made on the data collection instrument. The piloted participants finding were not included on the final study results. Throughout the data collection process, close supervision was made by the principal investigator. The collected data were checked regularly for completeness and consistency.

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 chemotherapy associated thromboembolic events among patients treated for solid malignancy. All potentially relevant variables were included in multivariable logistic regression. P-value < 0.05 was considered as statically significant.

Ethical Considerations
Prior to study initiation, informed consent was waived by Addis Ababa University, School of Pharmacy, ethical review board. The board thoroughly reviewed the study proposal on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guideline (approval number: ERB/SOP/52/03/
Also, permission to conduct the study was taken from the oncology department of Tikur Anbessa Specialized Hospital. Only numerical identifications were used as a reference. Confidentiality and anonymity of subject were maintained by not recording identifying details, such as name or any other personal identifiers.

Results

Baseline Characteristics

The median age of study participants was 43 years (range: 18-83 years) and the mean age in years was 43.56 (SD: 14.56). Most 216 (51.1%) were females. From the study participants, 3 (1.4%) were pregnant and 47 (11.1%) of them were smokers (Table 1).

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 1/3rd of the study participants had unknown or undocumented history about their comorbid diseases. HIV infection was 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 2).

Regarding, the Khorana risk score, more than half 235 (55.6%) of them were categorized as intermediate risk (Table 3, Figure 2).

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 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-Fluorouracil (5-FU) (Table 5).

Hormonal Therapy

Among the study participants around 1/4th of them used hormonal therapy and tamoxifen was the most frequently used 60 (60%) followed by Anastrozole 37 (37%). 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.

Incidence of Thromboembolic Events

Among study participants, VTE events encountered in 43 (10.2%) of them and DVT accounted the highest proportion (85.7%) (Figure 3). 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.

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

Predictive Factors Associated with Venous Thromboembolic Events

Of the included variables in multivariable logistic regression, only blood transfusion, a primary site of cancer and performance status were identified as independent predictors of VTE events.

![Figure 2](image_url)  
Khorana risk score of study participants of patients attending in adult oncology unit of TASH, Addis Ababa, Ethiopia, from January 2018- January 2019.

Table 3. 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 10 g/dl or use of red cell growth factors | 1           |
| Pre chemotherapy WBC count more than 11,000 cells/ml | 1           |
| BMI: 35 kg/m² or more                    | 1           |

BMI, Body Mass Index; WBC, White Blood Cell

Table 4. 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)              |
specific chemotherapy regimen

| 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)               |
| Cyclophosphamide                                                  |                        |
| 5-FU + Folic 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)              |
| Paclitaxel for 4 cycles.                                          |                        |
| Cisplatin                                                        | 6 (1.4)                |
| Folic acid + 5-FU + Irinotecan                                    | 5 (1.2)                |
| Cisplatin + Etoposide                                             | 5 (1.2)                |
| Cisplatin + Etoposide + Bleomycine                                | 5 (1.2)                |
| 5-FU + Folic acid + Oxaliplatin (FOLFOX)                          | 4 (1.0)                |
| 3 cycles + 5-FU + Folic acid + Irinotecan (FOLFORI) for 3 cycles  | 4 (1.0)                |
| Cisplatin + 5-FU for 6 cycle + Carboplatin + Paclitaxel for 2 cycles. | 4 (1.0)                |
| Paclitaxel for 2 cycles.                                          |                        |
| 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 for 6 cycle.                                           |                        |
| Paclitaxel                                                        | 2 (0.5)                |
| Others                                                            | 29 (6.85)              |

*Each patient was 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, dacearbazine, doxorubicin + cyclophosphamide + paclitaxel for 8 cycles followed by carboplatin + paclitaxel for 6 cycles, doxorubicin + 5-FU, carboplatin + 5-FU, epirubicin + Cisplatin + 5-FU, docetaxel 3 cycles, doxorubicin + cisplatin 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 carboplatin 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.

status showed statically significant association. The odds of VTE events in patients who did not undergo blood transfusion at a time of chemotherapy administration was reduced by 63% (AOR = 0.37, 95% CI: 0.16-0.89, p: 0.026) compared to their counterparts.

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 VTE (AOR = 10.64, 95% CI: 1.083-12.4573, p: 0.043) compared to patients treated for breast cancer.

In addition, ECOG performance score showed a significant association with VTE events in patients with ECOG score of 2 and 3-4, (AOR = 38.11, 95% CI: 7.60-49.090, p < 0.0001) and (AOR = 2.71, 95% CI: 1.12-6.54, p: 0.026) respectively had increased risk of developing VTE as compared to patients with ECOG score of 0-1 (Table 7).

**Discussion**

To our knowledge this retrospective cross-sectional study is the first of its kind in Ethiopia which gives insight into incidence and associated factors of chemotherapy associated VTE among patients treated for solid malignancy at adult oncology unit of TASH, Ethiopia.

Including patients who took at least one cycle of chemotherapy and four weeks of follow up for the development of VTE in patients receiving chemotherapy was chosen in this study based on previous related literatures done elsewhere. Moreover, it seems a reasonable follow-up period for capturing most, if not all, events occurring as a result of the drug intervention. It was observed that there was a high incidence of VTE events (10.2%) during the period of administration or within four weeks of completion of treatment Similar to studies done in different parts of the world: Pakistan 10.5%, University of Michigan (USA) 11.6%, both in Chicago (USA) and United Kingdom and 13.8% McMaster University (a multi-institutional retrospective analyses). The incidence of VTE in the present study was 10.2%. On the contrary some other studies have reported a higher rate of VTE among cancer patients treated with chemotherapy. For example a study done in the United Kingdom reported a 21% of VTE. The reason for this higher incidence rate could be an increased detection of VTE 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 VTE. In addition, the true incidence may even be higher as the study might have failed to detect every patient with VTE events because of its retrospective nature. This also supported by high treatment default rate in the center that among a cohort of 1149 patients, only 48.7% of them completed their treatment.

Lower VTE incidence was reported in the Jordan study (6.6%) and study conducted in Italy (6.6%). Most of the study participants in the Jordan study were classified as lower risk for VTE and this could be the explanation for lower rate of VTE. 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 VTE were found to be DVT. The finding of this study was in line with several studies done elsewhere, which ranged from 74 to 87.2%. In contrary, lower proportion of DVT were reported in the studies conducted in United Kingdom (17.56%). Australia (63.6%)

---

6 Clinical and Applied Thrombosis/Hemostasis
The lower rate of DVT could be due a significant number of study participants in these studies were grouped into the low-risk category of Khorana risk score, and USA (6.3%). The lower rate of DVT could be due a significant number of study participants in these studies were grouped into the low-risk category of Khorana risk score. Moreover, the variation might be, some of the studies included those patients who didn’t started chemotherapy, which was thought as one of the risk factors for VTE.

In the present study, PE accounted 2.4% of VTE and was comparable with a study conducted in the USA (7%). However, a significantly higher PE rates were reported almost in all other studies conducted from Pakistan (21.4%), United Kingdom (21.62%), Jordan (26%) and a multicenter study (33.3%). These variations might be due a weak record-keeping system in our institution and associated higher mortality rate of PE before the detection or diagnosis. Moreover other reasons of higher PE incidence rates could be, in some of these studies, patients had prolonged hospitalization and multiple risk factors for PE (BMI ≥ 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). Another explanation for such varied result may be in these 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%). However, it was higher than a study conducted in USA which ranged from 8.2% to 9.4%. In contrary relatively higher incidences were reported in a study done in Canada (20.0%). This difference might be, in the Canadian study 70% of VTE’s occurred at a coldest months of the year. This means the weather by itself could be a confounding factor. Also, compare to this study, most of the study participants in the Canadian study were at an advanced age and they received a longer duration of a chemotherapy course. On the other hand lower rates of MI incidences were reported in United Kingdom (2.7%) and in another multi-centered study (6.9%). Moreover, in some studies, combined VTE’s on a single patient had been seen. A study from Jordan reported around...
5.8% of VTE’s were PE plus DVT. In another study, there was 2.6% combined arterial thrombosis with DVT. Unlike these, no combined VTE has been documented in this study which may be due to inadequate documentation and poor record-keeping system.

Since VTE is associated with significantly higher mortality and morbidity, identifying predictors of chemotherapy associated VTEs in patients treated for solid malignancy is crucial. It helps to identify and prevent patients who are liable for such events and to increase practitioner concern regarding risk of VTE and consider thrombo-prophylaxis in high-risk patients as well.

Table 7. 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 (1.083-12.4573)* |
| Other                            | 11 (16.92)      | 54 (83.07)        | 1.075 (0.473-2.44)   | 1.54 (0.479-4.952)  |
| Performance Status               |                 |                   |                      |
| EOG 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 (7.609-49.0902)* |
| 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) |
| Regimen containing 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)  |
| Regimens congaing 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)  |

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

In another study, there was 2.6% combined arterial thrombosis with DVT. Unlike these, no combined VTE has been documented in this study which may be due to inadequate documentation and poor record-keeping system.

Since VTE is associated with significantly higher mortality and morbidity, identifying predictors of chemotherapy associated VTEs in patients treated for solid malignancy is crucial. It helps to identify and prevent patients who are liable for such events and to increase practitioner concern regarding risk of VTE’s and consider thrombo-prophylaxis in high-risk patients as well.

Similar to some other studies, history of blood transfusion while taking chemotherapy, the primary site of the tumor with GI malignancy and performance status showed a statistically significant association with the development of VTE. All these associations have been already observed in different studies and that they are consistent with what we know as they are independent risk factors of VTE and might have additive effect.

Advanced stage of cancer (metastasis disease), type of chemotherapy regimen, Khorana risk score, age, overweight or obesity and CVC, often thought to be predictors of VTE, were not found to play a role in our study. Similar to our study, previous studies also reported as there was no statistically significant association between age, sex, race, staging, Khorana risk score, type of chemotherapy regimen, BMI and CVC, and the occurrence of VTE.

In recent literature, a specific group of chemotherapies such as platinum analogs and fluorinated pyrimidine’s showed a significant association with the occurrences of VTE. Hence an attempt has been made whether such associations are present in our study. In doing so, we classify chemotherapy regimens into...
platinum’s and fluorinated pyrimidine’s analog containing regimens; 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 the prospective cohort study design nature of the Pakistan study favors in order to explore this kinds of association.

As a limitation, due to the retrospective cross-sectional nature of the study, there is still a chance that we might have missed some patients with VTE and was fully dependent medical records. The study conducted on a single-center; hence generalization to other patients treated for cancer in other recently opened centers may not be possible. Hence, future longitudinal prospective studies are needed to properly document the real incidence of chemotherapy associated VTE among patients treated for solid malignancy. Besides, the study had no control group to differentiate between effects of all the independent variables on the incidence of chemotherapy associated VTE.

Conclusion
The incidence of chemotherapy associated VTE among patients treated for solid malignancy was comparable to other studies done elsewhere. The most common type of VTE was DVT. Poor performance status, blood transfusion and patients treated for GI malignancy were significantly associated with the occurrence of VTE.

Acknowledgments
The authors would like to thank the archive units of adult oncology center at Tikur Anbessa Specialized Hospital and data collectors for their support throughout the study period. We would also like to forward our gratitude to Addis Ababa University for the financial support for the data collection. Moreover, the authors acknowledge that the MSc thesis from which this manuscript is extracted is available online on Addis Ababa University electronic thesis repository at http://etd.aau.edu.et/handle/123456789/21619. Moreover, online poster entitled “Thromboembolic Events Among Cancer Patients Treated with Chemotherapy at Adult Oncology Unit of Tikur Anbessa Specialized Hospital: A Retrospective Study” has been presented Conference: ISPOR, January 2021.

List of Abbreviations
BMI: Body Mass Index; CVC: Central Venous Catheter; DVT: Deep Venous Thrombosis; ECOG: Eastern Oncology oncology group; 5-FU: 5-Fluorouracil; FOLFIRI: 5-FU, Folinic Acid and Irinotecan; FOLFOX: 5-FU, Folinic Acid and Oxaliplatin; GI: Gastrointestinal; MI: Myocardial Infarction; PE: Pulmonary Embolism; TASHI: Tikur Anbessa Specialized Hospital; VTE: Venous Thromboembolism and White Blood Cell.

Consent for Publication
Not applicable.

Availability of Data and Materials
All the data and materials used in this paper are available from the corresponding author upon reasonable request.

Authors’ Contribution
ABY, AMF and SUH carried out conceptualization of the research, visualize and validate the study design, performed the statistical analysis; write, review and edit both the original draft and final manuscript. ABY also collected the data. WT participated in the conceptualization and visualization of the study design and statistical analysis. All authors read and approved the final manuscript.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
https://orcid.org/0000-0002-5203-5016

References
1. Sm A, Yilma Z, Assefa M, Tigenew H. Trends of breast cancer in Ethiopia. Int J Cancer Res Mol Mech. 2016;2(1):2-6.
2. Kifle M, Abdella K, Moges T, Tsegaye A, Beyene A. Disease prevention and control directorate. In: Federal Ministry of Health. 1st ed. SAGE, 2016. p. 1-85.
3. Camacho R, Neves D, Piñeros M, et al. Prescription of cancer treatment modalities in developing countries: results from a multicentre observational study. J Cancer Ther. 2014;5(11):989-999.
4. Maraveyas A, Waters J, Roy R, Fyfe D, Popper D, Lois F. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2011;48(9):1283-1292.
5. Greco PS, Bazzi AA, Mclean K, et al. Incidence and timing of thromboembolic events in patients with ovarian cancer undergoing neoadjuvant chemotherapy. Am Coll Obstet Gynecol. 2017;141(1):1-7.
6. Pant A, Liu D, Schink PJ, Lurain J. Venous thromboembolism in advanced ovarian cancer patients undergoing frontline adjuvant chemotherapy. Int J Gynecol Cancer. 2014;24(6):1002.
7. Papaxoinis G, Kopoulos K, Germetakis T, et al. Predictive factors of thromboembolic complications in patients with esophageal adenocarcinoma undergoing preoperative chemotherapy. Acta Oncol (Madr). 2018;57(6);1-9.
8. Reni M, Cescini B, Barni S, et al. Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients. Ann Oncol. 2007;18(10):1660-1665.
9. Meintadi MT, Sleijfer DT, Hoekstra HJ, Van Gessel AL, Van Roon AM. Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. J Clin Oncol. 2005;23(36):9130-9137.
10. Khorana AA. Risk assessment and prophylaxis for VTE in cancer patients. J Natl Compr Cancer Netw. 2011;9(7):789-798.
11. Gallus S, Cimminiello C, Apolone G, et al. A prospective study on survival in cancer patients with and without venous thromboembolism. Intern Emerg Med. 2013;9(5):1-9.

12. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Am Socity Hematol. 2018;9(12):1712-1724.

13. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol. 2018;24(3):1-7.

14. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy. J Clin Oncol. 2011;29(25):1-8.

15. McClure LA, Zakai NA. Racial differences in venous thromboembolism. J Thromb Haemost. 2011;9(10):1877-1882.

16. Zakai NA, McClure LA, Judd SE, et al. Racial and regional differences in venous thromboembolism in the United States in three cohorts. Natl Inst Heal Public Access. 2014;129(14):1502-1509.

17. Crous-Bou M, Harrington LB, Kabrhel C. Environmental and genetic risk factors associated with venous thromboembolism. Heal Hum Public Access. 2017;42(8):808-820.

18. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123(1):S11-S17.

19. Niguse H. Reasons for antiretroviral drug switch among patients attending at the antiretroviral therapy clinic of Tikur Anbesa Specialized Hospital. Addis Haftom Niguse (B. Pharm) A thesis submitted to the Department of Pharmacology and Clinical Pharmacy. TASH; Addis Ababa, 2016.

20. Woldeamanuel YW, Girma B, Teklu AM. Cancer in Ethiopia. Vol. 14, Lancet Oncology. 2013.

21. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol From Bed to Bench. 2013;6(1):14-17.

22. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Am Soc Hematol. 2016;111(10):4902-4908.

23. Zahir MN, Shaikh Q, Shabbir-Moosajee M, Jabbar AA. Incidence of venous thromboembolism in cancer patients treated with cisplatin based chemotherapy — a cohort study. BioMed Cancer. 2017;17(57):1-8.

24. Duivenvoorden WCM, Daneshmand S, Canter D, et al. Incidence, characteristics and implications of thromboembolic events in patients with muscle invasive urothelial carcinoma of the bladder undergoing neoadjuvant chemotherapy. J Urol. 2016;196(6):1627-1633.

25. Feuchtner J, Mathewos A, Solomon A, et al. Addis Ababa population-based pattern of cancer therapy, Ethiopia. PLoS One. 2019;14(9):1-12.

26. Abdel-razeq H, Mansour A, Abdelelah H, et al. Thromboembolic events in cancer patients on active treatment with cisplatin-based chemotherapy. Thromb J. 2018;16(2):1-7.

27. Piotr C, Malcolm M, Ian T. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. Am Urol Assoc. 1998;22(1):2021-2024.

28. Blom JW, Vanderschoot JPM, Oostindiër MJ, Osanto S, van der Meer FI, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66 329 cancer patients : results of a record linkage study. J Thromb Haemost. 2006;4(1):529-535.

29. Abdel-Razeq H, Albadainah F, Hijjawi S, Mansour A, Treish I. Venous thromboembolism (VTE) in hospitalized cancer patients : prophylaxis failure or failure to prophylaxis !. J Thromb Thrombolysis. 2011;31(1):107-112.

30. Abdel-Razeq H, Mansour A, Saadeh SS, et al. The application of current proposed venous thromboembolism risk assessment model for ambulatory patients with cancer. Clin Appl Thromb. 2017;24(3):1-5.

31. Bright T, Price T, Thompson SK, Watson DI. Venous thromboembolism in patients with esophageal or gastric cancer undergoing neoadjuvant chemotherapy. Int Soc Dis Esophagus. 2016;30(2):1-7.