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Original Article

Assessment of patient characteristics in cancer-associated venous thrombosis in Türkiye (CAT-TR study)

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Abstract

Aim: In cancer patients, the overall risk of venous thromboembolism (VTE) is increased 7-fold, and in cases of certain malignancies, this risk increases to 28-fold. The main objectives of this study are to describe patterns of use of anticoagulants for the treatment of cancer-related VTE in Türkiye and to assess patient characteristics.
Material and Methods: This was a multicenter, retrospective, descriptive study utilizing data from 17 centers across Türkiye. We included 2936 patients with a diagnosis of any cancer and a diagnosis of proximal lower-limb deep vein thrombosis (DVT) and/or pulmonary embolism (PE) between January 1, 2016, and December 31, 2019. These patients were only included if the cancer diagnosis was made at least 6 months before the diagnosis of VTE or within 30 days following the diagnosis of VTE. Patients were followed from the day after the index date until the earliest date among the dates of death, the end of the study, or the end of the 6-month treatment period.
Results: The study included 2796 patients with VTE between 2016 and 2019. While 41.4% of the participants were female, 58.6% were male, and 66.1% of the patients had DVT while 45.2% had PE. Furthermore, 52.7% had a history of smoking and only three patients had known hereditary thrombophilia. Lung cancer was the most common type of cancer, diagnosed in 872 patients (29.3%), followed by colon cancer diagnosed in 255 patients (8.6%) and breast cancer diagnosed in 202 patients (6.8%). Among these patients, 70.3% were in an advanced stage of the disease. Chemotherapy was administered to 469 (65.7%) patients at the time of disease onset. Among the patients with VTE, 99.5% were treated, and low-molecular-weight heparin was used in 97.5% of these cases while 3% of the patients were treated with direct oral anticoagulants. Bleeding was observed in 1.6% of the patients who participated in this study, and 39.1% of the bleeding events whose type was specified were categorized as major bleeding. Bleeding was most intense in the gastrointestinal tract (56.7%). Recurrence was observed in 1.5% of the patients and improvement was observed in 42.1%. In the first 6 months after diagnosis, 14.3% of the patients died. Causes of mortality could not be obtained from the patients' records.
Conclusion: VTE is common in patients with active cancer and associated with high recurrence and mortality rates. Efforts are needed to prevent VTE, diagnose it in time, and reduce the recurrence rates, especially in the first year after VTE diagnosis.

Keywords: Deep vein thrombosis, deep venous thrombosis, pulmonary embolisms, pulmonary thromboembolism, thromboembolism, venous

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INTRODUCTION

It is known that the risk of developing venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is significantly higher among patients with cancer than in the general population [1]. The French physician Armand Trousseau described the relationship between VTE and cancer in a seminal book published in 1865 [2].

Cancer is responsible for 18% of all VTE cases [2]. In cancer patients, the overall risk of VTE is increased by 7-fold, and in cases of certain malignancies, this risk increases to 28-fold [3]. VTE is the second leading cause of death in patients with cancer [4]. Not only VTE episodes themselves but also the complications of VTE, such as post-thrombotic syndrome, recurrent VTE, and chronic thromboembolic pulmonary hypertension, have negative impacts on the patient's quality of life [2,4].

VTE risk varies according to the type of cancer, the stage of the disease, and the treatment. It is more frequent in cases of metastatic disease compared to locoregional disease. Large epidemiological studies using hospital administrative data showed that patients with ovarian, brain, and pancreas cancer had the highest incidence rates of symptomatic VTE. Chew et al. investigated VTE incidence in patients with the 12 most common cancers and reported that patients with metastatic pancreas cancer had the highest risk of VTE (20 cases/100 patients/year) [5].

The treatment of VTE in cancer patients is controversial. The main aim of VTE treatment is to prevent PE, chronic thromboembolic pulmonary hypertension, VTE recurrence, and post-thrombotic syndrome. The recent approval of several direct oral anticoagulants (DOACs) provides clinicians new opportunities in the treatment of cancer-associated VTE, which was previously limited to parenteral agents and vitamin K antagonists. However, the treatment of VTE in cancer patients entails potential risks due to the additional pathologies of cancer and chemotherapy. To identify these potential risks, registry studies evaluating the characteristics and clinical outcomes of cancer patients with VTE have been conducted in different countries [5-9]. However, in the literature, we did not encounter large-scale studies on this subject conducted in Türkiye. Therefore, there is a need for comprehensive national data on the characteristics and clinical outcomes of cancer patients with VTE.

In this study, we aimed to present the characteristics and clinical and treatment features of cancer patients with VTE included in the Cancer-Associated Venous Thrombosis in Türkiye (CAT-TR) study, which provides national registry data.

MATERIAL AND METHODS

This study was carried out as a multicenter retrospective descriptive study. Following the principles set forth in the Declaration of Helsinki, the study received approval from Başkent University's Non-interventional Clinical Research Ethics Committee (Date: 04.11.2020, Number: 20/118). In previous studies conducted with cancer patients, the prevalence of VTE has been reported to range between 1% and 45% [10]. Thus, when the proportion of cancer patients with VTE was assumed to be 20%, it was determined that the sample size should be at least 1536 patients, with 2% precision and a 95% confidence interval (CI). The sample size was calculated using the following formula: $n=(Z^2\times P\times(1-P))/d^2$, where Z is a value from standard normal distribution corresponding to the desired CI (Z=1.96 for 95% CI), P is the expected true proportion, and d is the desired precision [11]. This study utilized a non-probability sampling method known as purposive sampling given its retrospective nature [12].

A total of 35131 patients with proximal lower extremity DVT, 27887 of whom had PE, were retrospectively examined for the presence of cancer in 17 centers located in different cities in Türkiye between January 2016 and December 2019. Cancer and VTE diagnoses were determined using the ICD-10 codes of C00-C97, 126, and 180-182 retrieved from the hospitals' electronic health record systems or the patients' files. Doppler ultrasound, venography, computed tomography examinations were required for the diagnosis of DVT and VTE. The inclusion criteria for the study were as follows: 1) being 18 years of age or older, 2) having received a cancer diagnosis at least 6 months before the diagnosis of VTE, or 3) having received a cancer diagnosis within 30 days after the diagnosis of VTE. Patients under 18 years of age and those without a cancer diagnosis were excluded from the study. After the exclusion process, 2936 patients with VTE who had a diagnosis of cancer were included in the study.

The management strategy for cancer-associated VTE is based on the latest guidelines of the National Comprehensive Cancer Network's Clinical Practice Guidelines in Oncology, the European Society for Vascular Surgery's Clinical Practice Guidelines on the Management of Venous Thrombosis, and the National Treatment Guidelines for Peripheral Artery and Vein Disease [13-15]. This study did not involve any contact with patients and did not affect the care that patients received. The outcome assessors were blinded to both the patients and the clinicians. De-identified patient data were compiled and analyzed to accomplish the proposed study objectives. The medical charts of all eligible patients were reviewed for the following data: demographic details including sex and age, weight, height, diagnosis, cancer type, cancer stage, treatment, date of diagnosis, baseline laboratory results, duration of anticoagulant use, type of VTE, resolution, recurrence, occurrence of bleeding, and mortality and, when applicable, the cause of mortality. Clinical and Laboratory Standards Institute guidelines were used to standardize laboratory values. The index date was set as the day of the VTE diagnosis and all patients were followed until the end of the 6-month treatment period or the date of death.

The primary endpoint variables of the study were the patients'

characteristic features and treatment patterns, while the secondary endpoint variables were recurrent venous thromboembolism, bleeding, and all-cause mortality.

Statistical Analysis

Normality distribution of the numerical data was determined with the Kolmogorov-Smirnov test and Q-Q plot. Under this assumption, the data exhibits a symmetrical bell curve, and 68%, 95%, and 99.7% of the data falls within mean±1 standard deviation (SD), mean±2 SD, and mean±3 SD, respectively [16]. Numerical variables that met the normality criteria were expressed as mean±SD, while those that did not were expressed as median (min-max). Frequency and percentage values were calculated for the descriptive statistics of categorical variables. All statistical analysis was performed using R Statistical Software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In 17 centers located in different provinces of Turkey, the prevalence of VTE was 8.3% (n: 2936) among 35131 patients with proximal lower extremity DVT. The study population includes a total of 2936 patients, 66.1% of whom had VTE and 45.2% of whom had PE. The majority of the patients were male (58.6%). Only three patients had known hereditary thrombophilia. In one of these patients, MTHR Heterozygous factor 13 was heterozygous positive. The basic characteristics of the patients are shown in Table 1.

Table 1. Distribution of demographic characteristics of the study population

Variables	All population n=2936	
	n	%
Gender		
Male	1215	58.6
Female	1721	41.4
Smoking		
Yes	1547	52.7
No	1389	47.3
Known hereditary thrombophilia		
Yes	3	0.1
No	2933	99.9
Comorbidities		
Hypertension	506	17.2
Chronic obstructive pulmonary disease	530	18.1
Coronary artery disease	84	2.9
Diabetes mellitus	292	9.9
Osteoarthritis	15	0.5
Atrial Fibrillation	129	4.4
Others	1280	43.6

Lung cancer was the most common type of cancer with 872 patients (29.7%), followed by colon cancer with 255 patients (8.6%) and breast cancer with 202 patients (6.9%). The cancer stage of VTE detected patients was mainly advanced period of metastases as high as 70% of stage IV. Chemotherapy±targeted therapy was administered to 469 (65.7 %) patients at the time of onset. Patients with cancer was at active stage and they were receiving treatment of cancer as radiotheraphy, surgical treatment, hormone and even immunotheraphy (Table 2).

Table 2. Background of patients: cancer types, stage and treatment

Variables	All population n=2936	
	n	%
Cancer type		
Lung cancer	872	29.7
Colon cancer	255	8.6
Breast cancer	202	6.9
Stomach cancer	161	5.5
Pancreas cancer	112	3.8
Ovarian cancer	99	3.4
Prostate cancer	84	2.9
Bladder cancer	74	2.5
Hematologic malignancy	55	1.9
Brain cancer	50	1.7
Uterus cancer	19	0.6
Others	990	33.7
Cancer stage		
Stage I	147	5.0
Stage II	238	8.1
Stage III	490	16.7
Stage IV	2064	70.3
Treatment		
Immuno-oncotherapy	6	0.20
Chemotherapy±targeted therapy	1929	65.7
Hormone therapy	85	2.9
Palliative treatment	41	1.4
Surgical treatment	534	18.2
Radiotherapy	291	9.9
Treatment naïve	50	1.7

It was determined that 99.5% of the patients received VTE treatment. VTE treatment was predominantly low-molecular-weight heparin (LMWH) (97.5%), followed by Enoxaparin (30.3%) and Bemiparin (30.3%). The distribution of VTE treatments are presented in Table 3.

Table 3. The rate of patients receiving VTE treatment and the distribution of treatment types

Variables	All population n=2936	
	n	%
VTE treatment		
No	14	0.5
Yes	2922	99.5
Direct oral anticoagulants	84	2.9
Apixaban	17	0.6
Rivaroxaban	55	1.9
Edoksaban	6	0.2
Dabigatran	6	0.2
Low-molecular-weight heparin	2850	97.5
Enoxaparin	1822	63.7
Bemiparin	880	30.3
Tinzaparin	148	5.4
Unfractionated heparin use	66	2.2
Thrombolytic agents	59	2.0
Vitamin K antagonist	44	1.5

Treatment Outcomes

Any bleeding was observed in 1.6% of the patients. It was found that 39.3% of the bleedings were major bleeding. The bleeding was more intense in the gastrointestinal tract (56.7%). Details regarding bleeding are provided in Table 4.

Table 4. Bleeding details

Variables	All population n=2936	
	n	%
Bleeding		
No	2889	98.0
Yes	47	1.6
Bleeding type		
Major bleeding	18	39.0
Non major bleeding	29	62.0
Bleeding Location		
Cutaneous	1	2.1
Genitourinary	11	21.0
Gastrointestinal	26	55.0
Lung	1	2.1
Others*	8	17.0

*Others: Vitreus, hematuria and fecal occult blood

Recurrence was observed in 1.5% of the patients in the study, and improvement was observed in 42.1%. 14.3% of patients died in the first six months after diagnosis. The causes of death could not be determined from the patient records.

DISCUSSION

This large 4-year VTE cohort had a maximum follow-up duration of only six months. This was a short-term investigation that did not allow us to describe the epidemiology of active cancer-associated VTE and of subsequent VTE recurrences accurately in a broad, unselected population. However, it allows us to make suggestions regarding the characteristics and treatment of patients with cancer-associated VTE.

The risk of VTE is higher among patients with cancer compared to the general population, bringing with it high mortality, morbidity, and costs. Approximately 5% to 20% of patients with cancer develop VTE and 20% of all VTE cases occur among patients with cancer [17]. In Türkiye, the 5-year prevalence rate of cancer was 581,286 in 2020 [18]. It has also been reported that 3% to 5% of patients in the early stage of cancer and 30% of patients with metastatic disease experience VTE; consequently, the minimum expected number of these patients is estimated as 18,000 in Türkiye [19]. From the records obtained over a 4-year period from 17 large centers specializing in cancer treatment, there are only 2936 cancer-related VTE cases, which is considerably low compared to the estimated ratio.

A higher incidence of PE has been reported in cancer patients compared to non-cancer patients [20]. In the present study, the rate of PE was 45% among a total of 2936 patients. Increasing age is a significant risk factor for VTE, which includes both DVT and PE. This risk is even higher in cancer patients compared to the general population [21]. Besides, smoking and comorbid conditions can increase the risk of VTE or PE. More than half of the patients included in this study were smokers, and a significant portion had comorbid conditions. Active smoking was previously associated with VTE events in patients with cancer [22]. Congestive heart failure, atherosclerosis and peripheral vascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, liver disease, renal disease, diabetes, obesity, alcoholism and alcoholism-related conditions, and hypertension were also reported as comorbidities in the Danish National Patient Registry study [23]. In addition to these risk factors, the increased request for diagnostic imaging, including lung imaging, especially in cancer patients with lung and abdominal cancer, may be associated with an increased incidence of PE.

In the current study, the most commonly observed type of cancer was lung cancer, followed by colon and breast cancer. These cancers may contribute more to the burden of cancer-associated VTE. This finding was consistent with hospital discharge data previously reported from the United States [20]. The other common cancer types were gastric, pancreas, and ovarian. Although other less common cancers are also reported to carry a high risk for VTE, their contributions to the VTE burden might be lesser due to their rarity [3,5,6]. Our findings support this

as lung, colorectal, and breast cancers are the most common malignancies in Türkiye [18].

There may be a bidirectional clinical relationship between VTE and cancer. Cancer increases the expression of procoagulant activities, contributing to the prothrombotic state in these patients, and the procoagulant activities may increase the rates of cancer growth, proliferation, and metastasis [2]. The risk of venous thrombosis for patients with distant metastases was found to be higher compared to patients without distant metastasis [3]. In our study, 70.3% of patients with cancer-associated VTE had distant metastases. It is known that the presence of distant metastases in cases of solid tumors increases the risk of venous thrombosis and it is much higher than the risk for patients with cancer without distant metastases. The presence of metastases is associated with increased hypercoagulability, and the hemostatic system seems to play a key role in the metastatic capacity of solid tumors [24,25]. In a Danish follow-up study, 55,000 cancer patients and 285,000 matched controls without cancer from the general population were followed. The risk of venous thrombosis among cancer patients appeared to be strongly associated with the stage of the cancer, with adjusted relative risks of 2.9, 2.9, 7.5, and 17.1 among patients with stage I, II, III, and IV disease, respectively [6]. In the California Cancer Registry study, increased venous thromboembolic events among metastatic cancer patients compared to patients without metastases were similarly reported for 12 different types of cancer and metastatic disease at the time of cancer diagnosis was found to be the strongest predictor of subsequent venous thrombosis [5].

Chemotherapy agents can trigger several mechanisms involved in the formation of VTE. Firstly, these agents can cause endothelial damage, leading to harm to the inner lining of blood vessels and initiating the clotting process. Additionally, chemotherapy can increase the release of thrombogenic substances, elevating the blood's viscosity, and promote platelet activation. Lastly, these treatments can slow down blood flow, facilitating clot formation especially in areas where the blood flow within the vessel slows down [26]. The majority of our patients (65.7%) were treated with chemotherapy and/or targeted therapy. The incidence of VTE may vary with different modalities of treatment, such as immunotherapy or tyrosine kinase inhibitors [27]. For cancer patients receiving chemotherapy and/or targeted therapy, the risk of VTE is significantly increased. The overall incidence of cancer-associated VTE has increased by 3-fold in recent years and even by 6-fold among patients receiving chemotherapy or systemic therapy. This increase might be explained by improved survival among cancer patients together with increased applications of chemotherapy and computed tomography scans for these patients [28]. Our sample included only two patients who had been treated by immunotherapy; therefore, we could not conduct analysis in this regard, but it is known that VTE is one of the most serious adverse effects of immunotherapy [29]. For instance, a study from the United States reported a higher risk of VTE for patients with cancer who underwent chemotherapy [30].

VTE is a multifactorial disease. Only three patients in this study had known hereditary thrombophilia. One of these three patients had the MTHFR heterozygous factor 13 heterozygous mutation. Although various genetic polymorphisms have been studied in relation to VTE predisposition in the general population, no clear evidence for predictive biomarkers could be found [31]. The risk of venous thrombosis in patients with cancer with the factor V Leiden or prothrombin 20210A mutation may be higher compared to patients with cancer without those mutations. Specifying this risk may help in determining high-risk groups and these patients can be given prophylactic anticoagulant therapy [32,33].

Only 0.5% of the patients in our study had not been treated, while 99.5% had been treated. Among the treated patients, 67.5% received LMWH. The most commonly used LMWH was enoxaparin (64.1%). On the other hand, 2.6% of the patients were treated with DOACs and the most commonly used DOACs were rivaroxaban and apixaban. The 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, which were based on a literature review conducted up to January 1, 2022, include guidance for patients with cancer and COVID-19. The key recommendations (grade 1A or 1B) are as follows: 1) LMWHs for the initial treatment (first 10 days) and maintenance treatment of cancer-associated thrombosis; 2) direct oral anticoagulants for the initial treatment and maintenance treatment of cancer-associated thrombosis for patients who are not at high risk of gastrointestinal or genitourinary bleeding in the absence of strong drug-drug interactions or of gastrointestinal absorption impairment; 3) LMWHs or DOACs for a minimum of 6 months to treat cancer-associated thrombosis or extended prophylaxis (4 weeks) with LMWHs to prevent postoperative venous thromboembolism after major abdominopelvic surgery for patients not at high risk of bleeding; and 4) primary prophylaxis of venous thromboembolism with LMWHs or DOACs (rivaroxaban or apixaban) for ambulatory patients with locally advanced or metastatic pancreatic cancer who have received anticancer therapy and have a low risk of bleeding. LMWHs as a class became the recommended first-line treatment for VTE in patients with cancer who have adequate renal function in all major treatment guidelines [34]. However, real-world data suggest that physicians have often prescribed warfarin and that patient compliance with LMWHs is low. For example, one study found that only 37% of patients prescribed LMWHs and 61% of patients prescribed oral agents were still continuing those treatments at 6 months [1]. In another study, it was shown that patients with any aspirin use had fewer VTE events (34.4%) compared to those without aspirin use [22]. In the study conducted by Akay et al.,

venous thrombosis in an upper extremity was commonly seen in cancer patients and treatment of DVT via DOACs was found to be more effective than LMWHs in preventing recurrent VTE (risk ratio: 0.111; 95% CI: 0.014-0.866) [35]. Therefore, DOACs can serve as the gold standard in the treatment of cancer-related VTE.

Bleeding was observed in 1.6% of the patients enrolled in this study. Of the bleeding episodes for which the type was specified, 39.3% were categorized as major bleeding. Bleeding was most intense in the gastrointestinal tract (56.7%). VTE recurrence was observed in 1.5% of the patients in this study and improvement was observed in 42.1%, while 14.3% of patients died in the first six months after diagnosis. Causes of mortality could not be obtained from the patients' records.

In the literature, it has been reported that patients with cancer-associated VTE have higher risks of bleeding complications during anticoagulant treatment and of recurrent venous thrombosis than patients with venous thrombosis but without cancer. In a Norwegian study that included 740 patients with a first venous thrombotic event, the 1-year case mortality rate was five times higher among patients with cancer-associated venous thrombosis (63.4%; 95% CI: 54.5-71.8) than venous thrombosis patients without cancer (12.6%; 95% CI: 10.1-15.5) [36]. In the RIETE Registry, with a large prospective cohort of over 35,000 patients with VTE, the 3-month mortality rate was much higher among patients with cancer-related venous thrombosis compared to venous thrombosis patients without cancer (26% vs. 4%, respectively) [37].

VTE is now considered a chronic disease, and the risk of recurrence remains elevated for many years after the initial event. A prospective follow-up study conducted by Prandoni et al. evaluated the risk of recurrent VTE or bleeding during anticoagulant treatment in 842 patients with VTE with and without cancer who were receiving anticoagulant therapy [38]. Among the 181 patients with cancer, the incidence of recurrent VTE was 20.7%, while it was 6.8% among those without cancer. The incidence of major bleeding was also increased more than 2-fold among patients with cancer (12.4% vs. 4.9%). Both VTE recurrence and bleeding were related to cancer severity and primarily occurred during the first month of anticoagulant therapy. These data reveal that many patients with cancer with an initial episode of VTE may require extended antithrombotic therapy; however, the risks of bleeding must be carefully weighed against the thromboprophylactic benefits associated with treatment and patients must be monitored closely for bleeding [38]. Patients with cancer-associated VTE were found to have a higher mortality rate and higher risk of bleeding compared to patients with isolated distal VTE without cancer [39]. The all-cause mortality rate was 64.5% and 88.1% at 1 year and 10 years, respectively, and mortality was higher among patients with both VTE and active cancer [40].

There are suitable algorithms to assist in the decision of initiating DOACs versus LMWHs. The rate of major bleeding with DOACs is similar to that of LMWHs and these events can be managed with transfusions and other standard measures. The patient's preferences should be considered and different approaches to LMWH injections should be explored for the success of treatment continuation without any delays. Gastrointestinal and genitourinary cancers have been shown to carry increased risks of major bleeding with DOACs. DOACs should particularly not be administered to patients with intact intraluminal tumors.

CONCLUSION

In patients with active cancer, VTE is common and associated with high recurrence and mortality rates. Assessments of patient- and cancer-related variables and patient preferences are key in determining an anticoagulant treatment that will appropriately balance the risks and benefits. Serious efforts are needed to prevent VTE, diagnose it in time, and reduce recurrence rates, especially in the first year after VTE diagnosis.

Ethics Committee Approval: Başkent University, Project Number:KA20382 Number: 20/108 Date: 04/11/2020.

Patient Consent for Publication: This is a retrospective descriptive study.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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