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Original Article

Risk factors for thrombosis risk in patients with cancer

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ABSTRACT

Aim: To evaluate the factors associated with Deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) in cancer patients.
Materials and Methods: A total of 237 cancer patients who underwent lower extremity venous Doppler Ultrasonography (USG) and/or pulmonary computed tomography angiography (PCTA) were included. Patients' demographic characteristics; chemotherapy data; immobilization status; use of central venous catheter; histories of 4-day-long bed rest, surgery within the last 6 months, long anesthesia for at least 2 hours, smoking, patients' laboratory tests, ABO blood group, PCTA and lower extremity Doppler USG results were retrospectively reviewed through the hospital information management system.
Results: The median age was 62 (age range 25 to 89). Thrombosis was detected in 83 patients according to the results of venous Doppler USG and/or PCTA of those patients who underwent imaging. Immobilization status (p=0.019), history of surgery within the last 6 months (p=0.02), anesthesia more than 2 hours (p=0.012) and 4-day-long bed rest (p=0.03) were found to be significantly associated with related risk of thrombosis. Additionally, thrombosis was found more frequently in the non-O group (especially group B) than in O group (p:0.024).
Conclusions: Besides well-known risk factors, blood group may be related with risk of thrombosis in the patients with the cancer diagnosis

1. Introduction

Venous thromboembolism (VTE) is the third most common vascular disease.[1] However, VTE more often develops in lower extremities, it also affects upper extremities, splenic veins, and cerebral veins. Increased risk of VTE was seen in cancer patients. The risk groups were defined as patient-related (age, ethnicity, obesity etc.), treatment-related (catheter, systemic chemotherapy etc.), and cancer-related (histological subtype, primary cancer site etc.) group.[2] In autopsy studies, the frequency of VTE was reported in half of the patients.[3] Malignant diseases lead hypercoagulant condition. Neoplastic cell causes direct activation of the coagulation system. It leads thrombin production to increase.[4–6] In addition, these patients usually have central venous catheters (CVC) that play a prominent role in this thrombotic event.[7] Patients with both VTE and malignancy have remarkably high morbidity and mortality. Therefore, determination of predisposing factors in cancer patients is very important to decide on prophylaxis and identify the thrombosis-related findings in high-risk groups.

In this study, our aim was to evaluate thrombosis frequency and factors related to thrombosis risk in the patients with cancer.

2. Materials and methods

Two hundred and thirty-seven patients with cancer and clinical suspected thrombosis or suspected thrombosis on follow-up pulmonary tomography and available lower extremity venous Doppler Ultrasonography (USG) and/or pulmonary computed tomography angiography (PCTA) images from January 2006 to December 2016, in Ankara University Medical Faculty Medical Oncology Department, were included in this study. Patients' demographic characteristics; chemotherapy data; immobilization status (patients with Eastern Cooperative Oncology Group performance status 4 was accepted as immobile; patients with Eastern Cooperative Oncology

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Group performance status 0, 1, 2, 3 was accepted as mobile); use of central venous catheter; histories of 4-day-long bed rest (duration of bed-rest after surgery), surgery within the last 6 months, long anesthesia for at least 2 h, smoking, patients' d-dimer value, hemoglobin, white blood count, neutrophil, lymphocyte, platelet count, liver and renal function test results, prothrombin time (PT), activated partial thromboplastin time (aPTT), ABO blood group, PCTA and lower extremity Doppler USG results were retrospectively scanned through the hospital information management system.

The Institutional Review Board of Ankara University School of Medicine has approved this study (EC confirmation code: 03-102-17). This study was performed according to Helsinki Declaration and good clinical practice.

Patients' baseline characteristics were described by using proportions for dichotomous and categorical variables. The Student t-test and non-parametric tests were used to assess the differences between continuous variables. Categorical variables were estimated with chi-square or Fisher exact tests. All analyses were evaluated by using SPSS 13.0 for Windows (IBM Corp., Armonk, NY). The *P* value of less than 0.05 was considered as statistically significant.

3. Results

One hundred and twenty three female and one hundred and fourteen male patients (52% and 48%, respectively) were enrolled to study and the median age was 62 (range 25–89). Gastrointestinal tract cancers (colorectal, stomach, esophagus, and pancreatic cancers, respectively), lung cancer and breast cancer were the most common cancers in patients whom thrombosis detected on (25.7%, 19.7%, and 18.1%, respectively) (Table 1).

VTE was detected in 59 of 163 patients who underwent lower extremity venous Doppler USG and 35 of 104 patients who underwent PCTA (radiographic findings consistent with pulmonary thromboembolism-PTE). Eleven patients underwent both Doppler Usg and PCTA. Totally, thrombosis was detected in 83 of 237 (35%) patients.

In our study, thrombosis was seen more often in males than females (% 60 vs. 40%, $p = 0.006$).

Fifty four patients were immobilized at the time of imaging and thrombosis was detected in 48% of immobilized patients, whereas thrombosis was detected in 30% of non-immobilized patients. Only 17.3% of the patients had undergone surgery within the last 6 months and thrombosis was detected in 56% of these patients. Thrombosis was detected in 47.3% of 55 patients who had a history of 4-day-long bed rest and 51% of the 45 patients who had anesthesia for at least 2 h. Finally, an association between increased risk of thrombosis and immobilization status ($p = 0.019$), histories of surgery within the last 6 months ($p = 0.02$), anesthesia for at least 2 h ($p = 0.012$), 4-day-long bed rest ($p = 0.03$) and hormonal treatment (p:0.03) were found statistically significant (Table 2). There was no relationship between thrombosis and the extent of disease, use of the central venous catheter, platinum-based chemotherapy, anti-VEGF treatment in our study population.

One hundred and eighty four patients' blood groups were detected. The relation between blood groups subtypes and thrombosis risk was evaluated. There was a statistically significant relationship between blood group subtypes and thrombosis (p:0.011). Thrombosis was found more frequently in the non-O group than in O group (p:0.024) (Table 2). When we stratified blood groups according to the presence of B antigens. It was shown that thrombosis was more frequent in B-group (p:0.036) when patients were stratified as B group (B and AB group) and non-B group (A and O).

Smoking history was evaluated as pocket-year and ≥40 pocket-year smoking history was associated with increased risk of thrombosis ($p < 0.05$). There was no significant correlation between d-dimer value, hemoglobin, white blood count, neutrophil, lymphocyte, platelet count, liver and renal function test results, activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombosis.

Table 1
Patients' demographic and clinical characteristics.

Age (years) (medyan/range)	62 (25–89)
Gender	(n)/(%)
Female	123 (52)
Male	114 (48)
Cancer type	(n)/(%)
Gastrointestinal	61 (25.7)
Lung	43 (19.7)
Breast	47 (18.1)
	(n)/(%)
Hormonal Treatment	33 (14)
Chemotherapy	199 (84)
Treatment with cisplatin	89 (37.6)
Treatment with any platinum	126 (53.2)
Anti-VEGF treatment	22 (9.3)

4. Discussion

VTE is an important cause of mortality and morbidity in cancer patients. The prognosis is worse when VTE develops in cancer patients. Heit et al. showed that VTE was higher in cancer patients compared to healthy people.[8] In previous studies, VTE rate in patients with cancer had been declared between 0.6% and 8%.[9]

Numerous studies showed an association between increased risk of thrombosis and smoking[10]; male sex,[11] immobilization status[11]; histories of surgery within the last 6 months,[12] anesthesia for at least 2 h, 4 day-long bed rest, indwelling catheter, type of cancer, extent of disease, platinum-based chemotherapy, anti VEGF treatment, hormonal treatment[11] and blood groups. Although smoking habit and male population were not shown as a risk factor in some studies, Cheng et al. and Wattanakit et al. determined the association between cigarette smoking and thrombosis[13,14] and Cushman et al. showed that thrombosis risk slightly higher in male population. Previous studies determined that any cause of immobilization had a risk of thrombosis 39%[15] and the risk of VTE after major surgery was increased by 2–4 times in cancer patients.[12,16] Some studies showed that there was an association between thrombosis and indwelling catheter.[7,17]

Numerous studies reported that the incidence of cancer-related VTE was quite high in pancreas, brain, stomach and ovarian cancer, but fairly low in prostate cancer, breast cancer and melanoma.[18–20] In some studies, it was shown that stage of disease was associated with increased risk of thrombosis. Thrombosis risk was shown as 3%–5% in patients with early-stage cancer and 30% in patients with advanced malignancy.[9] Previous studies showed that symptomatic VTE rates were shown to vary between about 11% and 75% depending on the chemotherapeutic agent type.[8,9,21] Cisplatin therapy is also one of the chemotherapy agents related to the increased risk of thrombosis. Moore et al. showed that DVT was seen in 49.7%, PTE in 25.4%, PTE and DVT in 13% of the patients receiving cisplatin-based therapy.[22] Kabbinivar et al. showed that

Table 2
Risk factors for thrombosis.

	Thrombosis n(%)	No thrombosis n(%)	*p* value
Gender			
Female	33 (27)	90 (73)	
Male	50 (44)	64 (56)	0.006
Hormonal Treatment	4 (12)	29 (88)	0.003
Chemotherapy	64(33)	134 (67)	0.082
Treatment with cisplatin	34 (38)	55 (62)	0.426
Treatment with any platinum	47 (33)	79 (67)	0.433
Anti-VEGF treatment	8 (37)	14 (63)	0.867
Immobilization			0.019
Yes	26 (48)	28 (52)	
No	56 (31)	126 (69)	
Central Venous Catheter			0.212
Yes	13 (27)	35 (73)	
No	69 (37)	119 (63)	
Undergone surgery within the last 6 months			0.002
Yes	23 (56)	18 (49)	
No	60 (31)	139 (69)	
Anesthesia at least 2 h			0.012
Yes	23 (51)	22 (53)	
No	60 (31)	132 (69)	
4-day long-bed rest story			0.03
Yes	26 (47)	29 (53)	
No	57 (31)	125 (69)	
Smoking			0.041
Yes	20(43)	27 (57)	
No	32 (31)	71 (69)	
D-dimer			0.072
≤1500	23 (32)	49 (68)	
>1500	37 (46)	43 (54)	
Blood Groups			
Non-0 & 0			0.024
Non-0	80(59)	55(41)	
0	38(78)	11(22)	
Non-B & B			0.036
Non-B	93(69)	42(31)	
B	25(51)	24(49)	

23% of patients treated with bevacizumab plus chemotherapy and only 6% of patients in chemotherapy control arm developed thrombosis.[23] Lower risk of thrombosis was detected with other anti-VEGF agents (sunitinib, sorafenib) in the literature.[24] Several studies reported that patients with breast cancer has an increased risk of DVT and PTE under tamoxifen therapy.[25]

Numerous studies showed that people with non-O blood types had a higher VTE risk compared to O counterparts. In the Longitudinal Investigation of Thrombophilia Etiology (LITE) study, it was observed that non-O blood type was independently related with the risk of VTE (odds ratio [OR] 1.64; 95% confidence interval [CI] 1.32–2.05).[26] In another study, it was observed that patients with non-O blood type had approximately 2 times increased risk of venous thrombosis.[27] There are also studies evaluating the relationship between cancer and ABO blood groups. Zhang et al. showed that blood group A was associated with increased risk of cancer, and blood group O was associated with decreased risk of cancer.[28] In our previous studies, we showed that there was no relationship between ABO blood group type and risk of aggressive prostate cancer, mesothelioma, and gastrointestinal stromal tumor. The risk of colorectal cancer and lung cancer was found to be associated with ABO/Rh blood groups as statistically significant[29–33]

In our study, VTE was detected in 83 of the patients (35%). We found that immobilization status; histories of surgery within the last 6 months, anesthesia for at least 2 h and 4 day-long bed rest, ≥40 pocket-year smoking; male sex, hormonal treatment, and ABO blood groups were defined statistically significant as risk factors for thrombosis. Our results are similar to the literature. Thrombosis risk was found to be higher in patients with B blood types than those in non-B blood types in this study. Our study differentiates with the population from other studies; in our study, the whole population consists of cancer patients.

In this study, there were no relationships between thrombosis and use of the central venous catheter, the extent of disease, type of cancer, platinum-based chemotherapy, anti-VEGF treatment in our study population. These results are incompatible with literature data. The insufficient number of patients in our study might have caused discordance.

Our study has a number of limitations. This study was retrospectively designed. The inability to reach sufficient patient information such as body mass index, prophylactic anticoagulant treatment, physical status or comorbidities might affect the predisposing factors.

In conclusion, determining predisposing factors in cancer patients is very important for assessing the VTE risk and for determining the patients who will take primary prophylaxis.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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