

Pattern of Venous Thrombosis in Cancer Patients: Frequency and Survival Effect; Single Center Experience

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Abstract Venous thromboembolism (VTE) represents one of the most important causes of morbidity and mortality in cancer patients. This investigation was undertaken to investigate the natural history of VTE in the oncology center in a tertiary care hospital. We did a retrospective study on cancer patients who presented to King Abdullah Medical city in Holly capital; a tertiary care hospital; from May 2011 to June 2013. Follow up period was calculated from time of VTE diagnosis till the last clinical visit or till patient death. Among 1,678 cancer patients, 132 (7.87 %) were diagnosed with VTE. The median patient age was 53.5 years, with female to male ratio 1.3/1. Thirty one patients (23.5 %) were diagnosed with VTE and cancer simultaneously, seventy four patients (56.1 %) were on chemotherapy and twenty eight patients (21.2 %) were on best supportive care. VTE were symptomatic in 110 patients (83.3 %) and asymptomatic in 22 patients (16.7 %). Lower limbs were the commonest site (42.4 %) with the highest incidence in patients with

advanced stages (93 %). Forty nine (37 %) patients were receiving LMWH as prophylaxis. Median survival in months for patients with VTE prophylaxis versus without prophylactic, and asymptomatic versus symptomatic were (12.6 vs 6.3; p 0.12 and 9.8 vs 12.4; p 0.885, respectively). There is underutilization of thromboprophylaxis in our region, which needs more effort to reduce VTE burden. Also we need large prospective studies to clarify the impact of VTE symptoms and presentation on patient's survival.

Keywords Venous thromboembolism · Cancer patient · Deep venous thrombosis

Introduction

Venous thromboembolism (VTE) is defined broadly to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT) and thrombosis in the other vascular territories. The association between VTE and malignancy was first reported by Armand Trousseau in 1865 and is supported by the results of more studies [1, 2]. In a population-based study, cancer was associated with a 4.1-fold greater risk of thrombosis, whereas the use of chemotherapy increased the risk 6.5-fold [3]. Virchow's triad of stasis, thrombophilia, and endothelial injury plays a critical role in the pathophysiology of VTE in patients with cancer. However, a second triad comprising changes in tumor biology, coagulation activation, and inflammation further describes the pathogenesis of thrombosis in the patient with malignancy [4].

It is unclear from available studies whether the risk of VTE is increasing for all cancers or only for specific subgroups of cancer patients. We hypothesized that the rate of

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VTE was increasing primarily in patients on active chemotherapy and was not because of increased diagnostic testing. Cancer sites, such as the pancreas, stomach, brain, lung, and metastatic disease are associated with higher rates of VTE in multiple studies [5–7].

The incidence of VTE in cancer patients has been difficult to determine due to the heterogeneity of the patient population [8]. Thus, identifying clinical characteristics that predispose cancer patients to increased risk of VTE is important to achieve better outcomes. There is limited data about VTE in cancer in Saudi Arabia; we undertook this study to evaluate the frequency, clinical pattern and outcome.

The primary end point of the current retrospective study was to evaluate the prevalence of VTE in cancer patients and the correlation with the demographic features, secondary end point was to evaluate the overall survival; in King Abdullah Medical City; a Saudi tertiary care hospital.

Materials and Methods

In our retrospective study, we reviewed medical records of cancer patients in King Abdullah Medical City—Holy Capital. We targeted patients during the period from May 2011 to June 2013.

The eligibility criteria were; age ≥ 18 years, pathological diagnosis of cancer, and objectively proven VTE. History of a thromboembolic event was determined on the basis of information in the patients' records at the primary medical evaluation and follow-up clinic visits. The following data were collected; the demographic features including (sex, age, marital status and residence), disease stage, timing of VTE in relation to cancer diagnosis either before or simultaneous or after it. The diagnosis of thromboembolic event was based on the clinical background; the presentation and by imaging studies; Doppler ultrasound, computed tomography and angiography.

Follow up period was calculated from time of VTE diagnosis till the last clinical visit at the time of data collection or till the death of patients.

Statistical Analysis

Data collected were analyzed using SPSS computer software. Continuous variables were summarized using mean, median, mode and standard deviation. Chi square test was used for categorical variables. Student's *t* test was used t-test for numerical data. Significance was defined as a *p* value of <0.05 . Multivariate logistic regression analysis was used to determine predictor variables that are associated with outcome.

Results

Patient Characteristics

We reviewed the medical record of 1,678 cancer patients (solid and hematology tumors) treated in KAMC oncology center during the study period. Demographic characteristics are summarized in Table 1.

The median age at the time of diagnosis was 53.5 years (range, 15–84 years), with female to male ratio of patients 1.3/1.

The VTE was categorized as symptomatic in 110 patients (83.3 %), and asymptomatic (discovered accidentally during routine radiological investigations and/or clinical judgment as documented in the files) in 22 patients (16.7 %).

There were 31 patients (23.5 %) with concurrently diagnosed VTE, 74 patients (56.1 %) during chemotherapy

Table 1 Patient characteristics

Parameters	Number	(%)
Age		
Median	53.5	
Range	15–84	
Gender		
Female	74	56.1
Male	58	43.9
Total	132	100
Relation between VTE and cancer diagnosis		
Simultaneous	31	23.5
After diagnosis	101	76.5
Total of treatment	132	100
Type		
Chemotherapy	74	56.1
Best supportive care	28	21.2
Others	30	22.7
Presentation of VTE		
Asymptomatic	22	16.7
Symptomatic	110	83.3
VTE prophylaxis		
Yes	49	37.1
No	83	62.9
Type of treatment		
LMWH	107	81.1
IVC Filter	11	8.3
Best supportive care *	14	10.6
Complications		
Bleeding	6	4.5
Thrombocytopenia	5	3.8

VTE Venous thromboembolism, LMWH low molecular weight heparin, IVC inferior vena cava

* No treatment modifying agents

and 28 patients (21.2 %) during the best supportive care period (No treatment modifying agents).

Of all VTE cases, only 37 % patients received prophylactic dose of low molecular weight heparin (LMWH), with 11 patients developed treatment related complications (six patients developed bleeding and five patients developed thrombocytopenia), where they managed by putting IVC filter.

Among the patients receiving chemotherapy, 4.41 % developed VTE which is greater than the rate observed in the rest of study group (3.5 %).

The basic features of asymptomatic VTE are summarized in Table 2.

Venous Thromboembolism

Among 1,678 cancer cases were treated during the study period, VTE was diagnosed in 7.87 %. The most common type of VTE was DVT in the lower limbs in 56 patients (42.4 %), followed by DVT in upper limbs in 32 patients (24.4 %), and PE in 16 patients (12.1 %). More details are shown in Table 3.

Table 2 Features of Asymptomatic VTE

Age	
Median	57.5
Range	17–83
Sex; females/males	10/12
Cancer type	
NHL(8), Sarcoma(1), CUP(2), pancreas(1), lung(1), cholangiocarcinoma (1), colon(1), germ cell(1), breast(1), HL(1), NPC(2), endometrium (1), melanoma (1).	
Type of thrombosis	
DVT lower limb	4
DVT upper limb	0
IVC	4
SVC	4
PV	3
PE	4
Mesenteric	2
Internal jugular	1
Timing	
At the same time of diagnosis	14
With treatment	8
Outcome	
A life	11
Died	11

CUP Carcinoma of unknown primary, HL Hodgkin’s Lymphoma, NPC nasopharyngeal carcinoma, DVT deep vein thrombosis, IVC inferior vena cava, SVC superior vena cava, PV portal vein, PE pulmonary embolism

Distribution of Underlying Malignancy Associated with VTE

The most common type of cancers associated with thrombosis were non-Hodgkin’s lymphoma, colon, acute leukemia, genitourinary and breast cancer. Majority of the patients (93 %) with VTE diagnosis had advanced stage of cancer. The type and stage of cancer are given in Table 4.

Survival Analysis

Log rank (Mantel-Cox) survival analysis was summarized in Table 5.

Figure 1, shows the survival curve for patients with symptomatic and asymptomatic.

Table 3 Type of thrombosis

VTE sites	Numbers (%)
Total numbers with DVT	132 (7.87)
DVT in lower limb	56 (42.4)
DVT in upper limb	32 (24.4)
PE	16 (12.1)
PE and DVT	5 (3.8)
Abdominal	
SVC	7 (5.3)
IVC	5 (3.8)
PV	3 (2.3)
Mesenteric	2 (1.5)
Internal jugular	6 (4.5)

DVT Deep vein thrombosis, IVC inferior vena cava, SVC superior vena cava, PV portal vein, PE pulmonary embolism

Table 4 Distribution of underlying malignancy associated with VTE

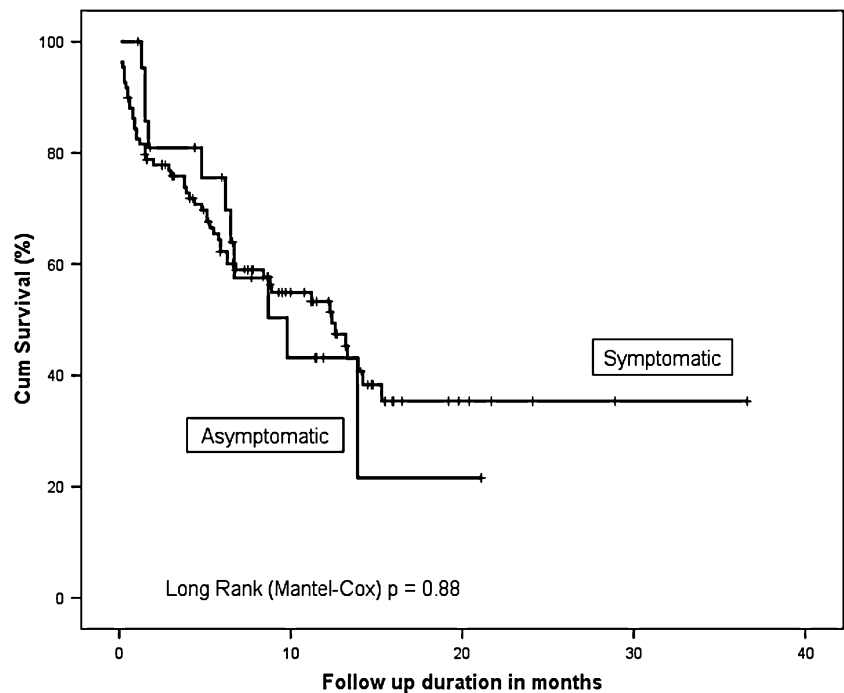
Type of cancer	Number	Early stage	Advanced stage
NHL	24	6	18
Colon	17	1	16
Acute leukemia	13	0	13
Genitor-urinary	16	0	16
Breast	15	1	14
Lung	11	0	11
Gastric	7	0	7
HL	5	1	4
Other GIT	5	0	5
OS	4	0	4
Others	15	0	15
Total	132	9 (7 %)	123 (93 %)

OS Osteosarcoma, NHL non Hodgkin’s lymphoma, GIT gastrointestinal tract

Table 5 Survival groups

	Number	(%)	Estimated median survival	P value**
Prophylaxis status				
Yes	49	40.8	12.6	0.12
No	83	56.6	6.3	
Presentation of VTE				
Asymptomatic	22	16.7	9.8	0.88
Symptomatic	110	83.3	12.4	

Fig. 1 Log rank (Mantel-Cox) survival analysis showed no difference in overall survival was found between symptomatic and asymptomatic patients ($p = 0.88$)



VTE (median survival 12.4 months vs 9.8 months, respectively; $p = 0.88$ with no significant difference). Also there is no difference in overall survival between patients with VTE prophylaxis versus no prophylaxis group (median survival 12.6 months vs 6.3 months, respectively; $p = 0.12$) as shown in Fig. 2.

Discussion

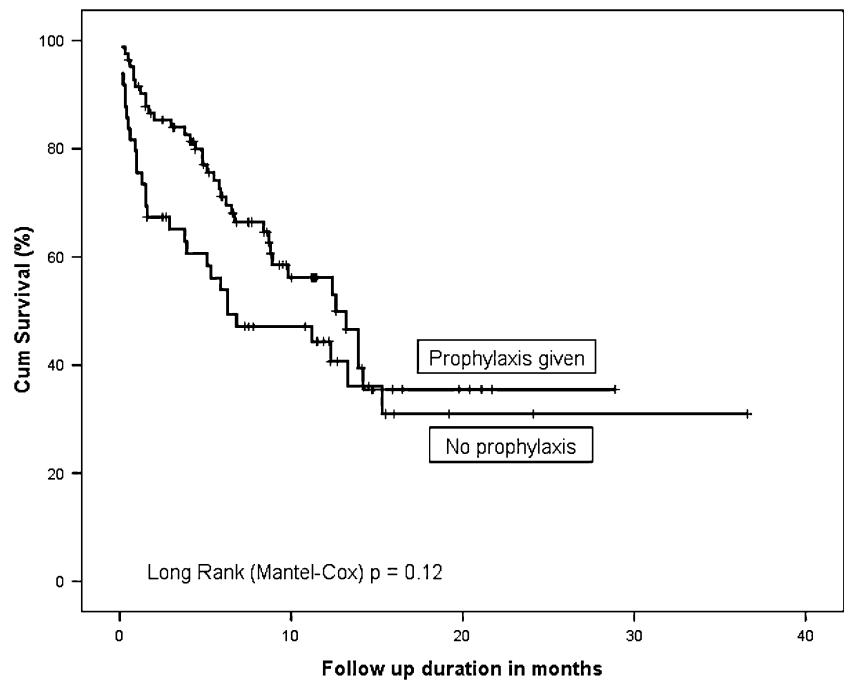
VTE represents one of the most important causes of morbidity and mortality in cancer patients. It has important implications on cancer patients; these include significantly worse survival, compromised quality of life, and increased the risk of bleeding complication following the use of anticoagulants, risk of recurrent VTE and additional burden on the resources [9].

To our knowledge, No population-based study has determined the incidence of VTE among patients diagnosed

with specific types and stages of cancer. Reported rates of VTE in cancer patients range from as low as 1.6 % to as high as 20 % [10–13]. In addition to this real difference, variations in these estimates may also depend on the study design, case definition, and age distribution. The rate of VTE in our study was not very high (7.9 %). However, we believe that the actual rate is much higher than our results. This may be due to the retrospective nature of the study in addition to death of some patients from cancer before diagnosis of VTE. Third, autopsies for diagnostic purposes are usually not carried out routinely in Saudi Arabia because of religious and cultural beliefs, so it is reasonable to believe that the actual rate of VTE in Saudi cancer patients is probably much higher than found in our study.

In our study, VTE was diagnosed in 31 patients (23.5 %) simultaneously with cancer diagnosis and incidentally during routine investigation which are frequently reported in other studies; in a retrospective cohort analysis by Moore et al., 44 % of all VTE events were incidental

Fig. 2 Log rank (Mantel-Cox) survival analysis showed no difference in overall survival was found between patients who have been given prophylaxis versus no prophylaxis group ($p = 0.12$)



diagnosed and in another cohort study by Singh et al., 50 % of DVTs and 35 % of PEs were incidentally discovered [14–19].

An important finding from our study is the presence of a considerable number of patients with asymptomatic thrombosis; 22 patients (16.7 %), and the majority of these patients had thrombosis in abdominal vessels; 13 patients (9.8 %) and four patients were found to have PE.

The high percentage of asymptomatic VTE raises the question of screening. There is much uncertainty about of which, if any, subgroups should be screened, and whether this would have an important impact on clinical outcome so, the routine screening for VTE in cancer patients till now is generally not recommended. In our center, we generally start by therapeutic dose anticoagulation for all cancer patients with asymptomatic VTE.

Another important finding from our study is the under utilization of thrombosis prophylaxis in cancer patients; only 49 patients (37.9 %) received medical prophylaxis. Several studies from around the world have consistently shown a lack of prophylaxis in hospitalized medical patients, including cancer patients [20, 21]. This is a particular problem in the developing countries but also a common observation even in the developed countries [22, 23]. There are several reasons that might explain why prophylaxis is not a widespread practice, include; failure to appreciate the risk of VTE in medical and cancer patients, complexity of existing risk assessment models, poor implementation and compliance with the guidelines, and cost issues.

Although VTE commonly occurs in patients with cancer, most oncologists underestimate both the prevalence of VTE and its negative impact. With this background in mind, The American Society of Clinical Oncology (ASCO) first published an evidence-based clinical practice guideline on prophylaxis and treatment of VTE in 2007 [24], and updated at intervals determined by an Update Committee in 2013 [25].

Given the underutilization of VTE prophylaxis in cancer patients, an integrated risk stratification checklist along with a pre-printed order sheet for VTE prophylaxis is a useful way of promoting its use, and should be part of the routine assessment of all cancer patients.

The impact of symptomatic VTE on survival is described in literatures [26, 27]. Sorensen et al. found that the 1-year survival rate for cancer patients with thrombosis was 12 % compared with 36 % in control patients ($p < 0.001$) [28]. This high mortality was thought to reflect deaths due to both thromboembolism and a more aggressive course of malignancies associated with VTE. In our study; 1-year survival rate for cancer patients with thrombosis was 18.9 %. Survival analysis showed no difference in overall survival between patients with VTE prophylaxis versus no prophylaxis group (12.6 months vs 6.3 months, respectively) ($p = 0.12$), which did not match with literatures. This can be explained by the difference in sample sizes, type or stage of cancer in addition to the retrospective nature of the study.

Also there was no difference in overall survival between symptomatic and asymptomatic patients (12.4 months,

9.8 months respectively; $p = 0.885$). To our knowledge, no long-term survival studies of patients with an asymptomatic VTE have been reported in the literature. Engelke et al. in a retrospective study found that those with an incidentally diagnosed VTE, despite failure to treat, had a benign prognosis [29]. This retrospective trial was also limited by small patient numbers, and the investigators recommended further assessment.

Limitations

The potential limitations of this study included the fact that information about some patients was incomplete in view of the retrospective nature of the study might have introduced some bias in our findings. Specifically, there was not enough information about chemotherapy type, radiotherapy, hormone therapy or targeted therapy.

Small sample size is also one of the most limiting factor, owing to the given sample size, one further limitation of the study is the low number of events when separating according to sites (abdominal, superficial, distal, proximal) or presentation (symptomatic, asymptomatic) DVT for outcome analysis. Therefore, larger prospective studies are needed to validate our findings and which are powered to detect differences in short-term survival between the above-mentioned subgroups of venous thrombosis. Furthermore, we did not measure recently published blood-based biomarkers, such as tissue factor which may be helpful in management of asymptomatic DVT.

Conclusion

Although the incidence of VTE in our region is not very high; it may be underestimated due to multiple factors, added to underutilization of thromboprophylaxis. Regardless of the cause, VTE in cancer patients is of considerable consequence, given its strong association with poor survival. Much work needs to be done to reduce the burden of VTE among cancer patients.

Ethical Consideration Ethical approval to conduct the study was taken from the IRB review committee before the commencement of the study.

Conflict of Interest The authors certify that is no potential or actual conflict of interest related to this research.

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