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INCIDENCE OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS IN NINEVEH PROVINCE

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ABSTRACT

Background: Cancer patients are at an increased risk of developing venous thromboembolism (VTE). VTE increases morbidity and mortality rates in cancer patients and differs by primary cancer type, stage of cancer, and type of Treatment. The reported incidence rate of VTE varies widely between studies due to differences in ascertainment and the underlying populations represented. This study aimed to find the VTE incidence rate and the related risk factors in Nineveh. **Methods:** A prospective cohort study was used to determine the incidence rate of VTE in cancer patients. Data was gathered between January 2022 and January 2023, and patients were followed for twelve months after cancer diagnosis. **Results:** A total of 1968 patients were eligible for analysis. The most common cancer type was breast cancer. Forty-six patients had VTE, and the 12-month cumulative of VTE was 2.3%. Smoking, distant metastasis, and receiving systemic chemotherapy were the most significant factors in developing VTE. One-third of patients with VTE had metastasis in comparison with 20% in the whole cohort. However, age and tumor types had no significant difference in risk for developing VTE in cancer patients. **Conclusion:** In Nineveh, breast cancer was the most frequent tumor found among the studied groups. The overall incidence of VTE was consistent with that reported in other studies in different countries. The risk of developing VTE in patients with cancers was influenced by receiving systemic chemotherapy and the stage of cancer. Smoking also increases the risk of VTE in the cancer population.

KEYWORDS: Cancer, Incidence, Venous Thromboembolism.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two common venous thromboembolisms (VTE) that cause fatalities in cancer patients. Chemotherapy is one of the variables that contribute to cancer patients' higher risk of VTE. Chemotherapy patients have a 6- to 7-fold increased risk of cancer-associated VTE because of direct effects on vascular endothelium.[1] Still, there are not many cancer patients who get thromboprophylaxis when undergoing chemotherapy.[2] Clinical recommendations currently lack clarity about the circumstances under which patients should receive primary VTE prophylaxis while undergoing chemotherapy.[3] Consequently, it is essential to keep an eye out for VTE in cancer patients receiving chemotherapy.

Genetics, tumor-derived variables, cancer type, and stage all influence VTE risk; the presence of metastases increases the risk of VTE by a factor of two. Individuals with malignancies of the brain, lung, uterine, bladder, pancreas, stomach, and kidney have the most significant

1-year incidence risk of VTE. Patients with metastases for these tumor types have a 4–13-fold higher chance of VTE than patients with localized illness.[4] Moreover, cancer treatments themselves may raise the possibility of developing VTE. VTE risk is increased by the use of hormone therapy or chemotherapy, the immobility brought on by surgical procedures, and the implantation of indwelling central venous catheters (CVCs).[5]

More than 20 guidelines on the prevention of VTE in hospitalized cancer patients have been published since 1986. The four organizations that have released the most well-known guidelines in recent years are the American Society of Clinical Oncology (ASCO) Guidelines on VTE published in 2015[6], the European Society for Medical Oncology [2011][5], the American College of Chest Physicians: Antithrombotic and Thrombolytic therapy guidelines [2012][7], and the 2015 National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology: Venous Thromboembolic Disease.[8]

Cancer and thrombosis are closely linked, with the relationship first described by Bouillard in 1823 and further elaborated by Trousseau in 1865.[9] Cancer increases the risk of thrombosis due to its ability to affect Virchow's triad, causing venous stasis, altering blood components like procoagulant factors, and leading to endothelial dysfunction. The pathogenesis of thrombosis in cancer involves changes in tumor biology, coagulation activation, and inflammation. Antiphospholipid antibodies, platelet activation, and reduced hepatic anticoagulant synthesis contribute to coagulopathy, while elevated D-dimer levels indicate chronic systemic coagulation activation.[9,10] Cancer genetics significantly influence VTE risk, with oncogenes like k-ras and mutations in p-53 causing increased expression of tissue factor (TF) by tumor cells. This promotes angiogenesis, tumor growth, and metastasis. In a retrospective cohort study, patients with increased tumor cell TF expression had a 6-fold higher VTE risk compared to those with low TF expression.[11] Cancer immunology highlights the role of inflammation in cancer, leading to the production of proinflammatory cytokines like interleukin-6, interleukin-8, and interleukin-10.[12] These cytokines promote thrombosis by increasing adhesion molecules on endothelial and monocyte surfaces. Circulating microparticles bearing TF, which are shed from various cells, are linked to a higher risk of vascular endothelial edema (VTE) in cancer patients. Patients with higher microparticle levels treated with anticoagulation showed a non-significant trend towards lower VTE rates.[12, 13]

Because of variations in underlying population representation and methods of assessment, the reported incidence of cancer-associated venous thromboembolism (VTE) varies greatly between studies (1.6% to 6%).[14] The incidence of VTE has been reported to have increased over time in several studies.[14,15] According to some researchers, the 12-month cumulative incidence of VTE during the last ten years has increased thrice.[14] Patients with pancreatic, lung, stomach, brain, and ovarian cancer have the highest chance of developing ventral tetraploid expression (VTE), according to most studies. The incidence of VTE varies significantly according on the initial tumor location.[14,16] Comorbidities, chemotherapeutic usage, and advanced age are further risk factors for VTE.[15] Patients who have metastatic cancer are recognized to have the highest risk of VTE.[16] Cancer stage is also strongly related with an elevated risk for VTE. Aside from age, comorbidities, and chemotherapy usage, additional variables that contribute to VTE.[15] Additionally, there is a clear correlation between cancer stage and an elevated risk for VTE; individuals who have metastatic illness are considered to have the highest risk.[16]

AIM: To find the VTE incidence and the related risk factors in Mosul Cancer Center.

METHODS

Study design and setting: A prospective cohort study was applied to find the incidence rate among 1968 cancer patients who enrolled in Mosul Oncology Hospital (MOH). All cancer types were included in this study.

Inclusion criteria: All patients diagnosed with malignancy treated in MOH from January 2022 to January 2023. Patients with inherited thrombophilia were excluded from the study. The patients were followed up with regular checks and investigations for the development of VTE.

Data collecting tools: The patients were interviewed by the researchers, and verbal consent for participation was taken before they were enrolled in the study. All data were recorded in questionnaire form, including the history, physical examinations, and investigations which were collected at the database time and at the regular follow-up intervals.

Statistical analysis: The data analysis was conducted using SPSS version 26. The Chi-square test with the fissure exact test was used instead of the Chi-square when any cell presented with an expected value of less than five statistical analyses. The p-value ≤ 0.05 is considered significant.

RESULTS

This study includes 1968 patients with different types of newly diagnosed cancer. These patients were followed up for one year, and forty-six of them developed VTEs. The cumulative incidence rate of VTE in this sample was 2.3% within one year after cancer diagnosis, as shown in Figure (1).

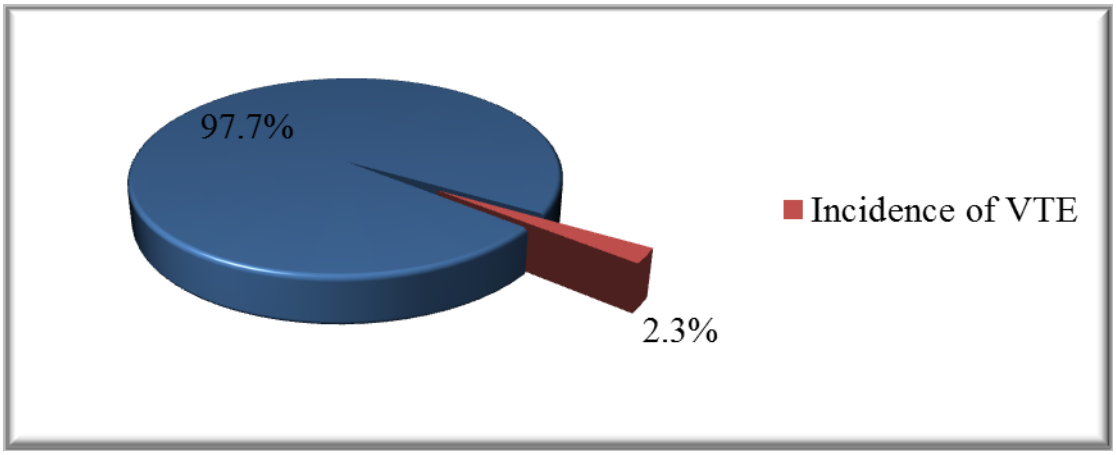

Figure (1): The overall incidence rate of VTE among the tumors.

The mean age among the VTE group was 60.70±15.77 years, with a range of 18.00-85.00 years, while among the non-VTE group, the mean age was 59.37±16.14; the difference was statistically not significant, as shown in Table (1).

Table (1): Comparison of mean age between the studied groups.

Age	VTE (n=19)	Non-VTE (n=27)	Total (n=46)	p-value*
Mean± SD	61.63±15.75	59.37±16.14	60.70±15.77	0.634
Mini.-Maxi.	15.0-85.0	25.0-83.0	18.0-85.0	
**t-test for independent means*				

The distribution of the study sample according to the type of tumor was demonstrated in Figure (2) and showed that the most frequent tumor was breast cancer at 17.4%, pancreatic cancer at 10.9%, and colon cancer at 8.7%.

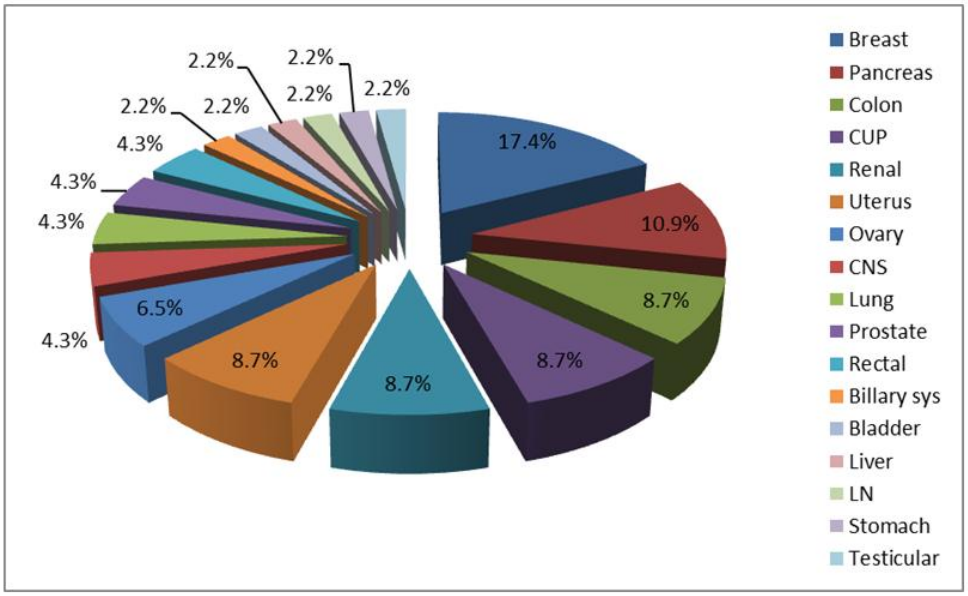

Figure (2): The distribution of the study sample according to the type of tumor.

A comparison of risk factors between studied groups was demonstrated in Table (2) and revealed that stage IV was the most frequent among both groups, with a statistically significant higher rate among the VTE group in relation to the non-VTE group (34.8% vs. 26.1%; p=0.007). Concerning smoking, 30.4% of the VTE group and only 4.3% of the non-VTE group were smokers, with a statistically significant difference (p=0.000). BMI, ECOG, family history of VTE, and central venous catheter history (CVCH) showed no significant differences.

Table (2): Comparison of risk factors between studied groups.

Risk factors		VTE (n=19) No.(%)	Non-VTE (n=27) No.(%)	Total (n=46) No.(%)	p-value*
Stage	1	1(2.2)	2(4.3)	3(6.5)	1.000*
	2	1(2.2)	5(10.9)	6(13.0)	0.377*
	3	1(2.2)	8(17.4)	9(19.6)	0.060*
	4	16(34.8)	12(26.1)	28(60.9)	**0.007****
BMI	<18	2(4.3)	0(0.0)	2(4.3)	0.165*
	18-24.9	5(10.9)	8(17.4)	13(28.3)	0.806**
	25-29.9	8(17.4)	11(23.9)	19(41.3)	0.926**
	≥30	4(8.7)	8(17.4)	12(26.1)	0.734*
ECOG	0	0(0.0)	1(2.2)	1(2.2)	1.000*
	1	2(4.3)	6(13.0)	8(17.4)	0.439*
	2	9(19.6)	11(23.9)	20(43.5)	0.655**
	3	7(15.2)	9(19.6)	16(34.8)	0.806**
	4	1(2.2)	0(0.0)	1(2.2)	0.413*
Smoking	No	5(10.9)	25(54.3)	30(65.2)	**0.000****
	Yes	14(30.4)	2(4.3)	16(34.8)	
Family history of VTE	No	16(34.8)	21(45.7)	37(80.4)	0.715*
	Yes	3(6.5)	6(13.0)	9(19.6)	
CVCH	No	16(34.8)	26(56.5)	42(91.3)	0.291*
	Yes	3(6.5)	1(2.2)	4(8.7)	
**Fisher Exact test; **Chi square test*					

The current study showed no statistically significant differences between the studied groups and each type of treatment's modalities except systemic chemotherapy, as shown in table (3).

Table (3): Comparison of Treatment Modalities between the studied groups.

Modalities of Treatment		VTE (n=19) No.(%)	Non-VTE (n=27) No.(%)	Total (n=46) No.(%)	p-value *
Surgery	No	5(10.9)	5(10.9)	10(21.7)	0.718
	Yes	14(30.4)	22(47.8)	36(78.3)	
Chemotherapy	No	6(13.0)	2(4.3)	8(17.4)	**0.050**
	Yes	13(28.3)	25(54.3)	38(82.6)	
Radiotherapy	No	14(30.4)	20(43.5)	34(73.9)	1.000
	Yes	5(10.9)	7(15.2)	12(26.1)	
Hormonal therapy	No	17(37.0)	21(45.7)	38(82.6)	0.439
	Yes	2(4.3)	6(13.0)	8(17.4)	
**Fisher Exact test*					

A Comparison of co-morbidities and types of treatment between the studied groups was demonstrated in Table (4). This table shows that there was no significant difference between the studied groups concerning the co-morbidities and types of treatment.

Table (4): Comparison of co-morbidities and types of Treatment between the studied groups.

Co-morbidities		VTE (n=19) No.(%)	Non-VTE (n=27) No.(%)	Total (n=46) No.(%)	p-value
No		7(15.2)	4(8.7)	11(23.9)	0.158*
Yes	DM	2(4.3)	2(4.3)	4(8.7)	
	HT&DM	1(2.2)	2(4.3)	3(6.5)	
	DM, HT & Stroke	1(2.2)	1(2.2)	2(4.3)	
	HT	6(13.0)	12(26.1)	18(39.1)	
	HT, AF& stroke	1(2.2)	0(0.0)	1(2.2)	
	HT+TIA	1(2.2)	0(0.0)	1(2.2)	
	HT& AF	0(0.0)	3(6.5)	3(6.5)	

	HT +MI	0(0.0)	1(2.2)	1(2.2)	
	HT & atrial fibrillation	0(0.0)	1(2.2)	1(2.2)	
	Hypothyroidism	0(0.0)	1(2.2)	1(2.2)	
Types of treatment	LMWH	11(23.9)	15(32.6)	26(56.5)	0.875**
	UFH	8(17.4)	12(26.1)	20(43.5)	
**Fisher Exact test; **Chi square test*					

DISCUSSION

Malignancy is well documented as increasing the risk of VTE development, specifically in metastatic settings.[17] In the current study, the 12-month cumulative incidence of VTE is 2.3% of all cancer patients. The mean age of patients in the present study who developed VTE was 61.63±15.75 years, while the mean age among the patients who did not develop VTE was lower. Similarly, in the overall population, the incidence rates for VTE increase after 60 years old.[20]

According to the findings of Mahajan *et al.*[19], whereby 22.2% of patients had breast cancer, 19.2% had prostate cancer, and 14.3% had lung cancer, the most common tumor in the current cohort was breast cancer, which was followed in frequency by pancreatic cancer. Lung (20.1%) and colorectal (13.4%) and breast (12.3%) cancers were the most prevalent tumor forms in individuals with VTE. Compared to 20% of the cohort as a whole, one-third of VTE patients developed metastatic illness.

Numerous studies examining the impact of local, regional, and distant cancer stages on the occurrence of VTE discovered that individuals with regional and distant metastases had a markedly increased chance of developing VTE in comparison to those with local illness.[26-29] With the exception of stage IV, the tumor stage in the current investigation did not significantly differ.

According to the White *et al.* research[24] the incidence of VTE was lowest in people with breast and prostate cancer and greatest in people with pancreatic, brain, ovarian, and lung cancer. According to Martens *et al.*[18], there was a substantial difference of up to six times across cancer subtypes in terms of the association between VTE and cancer type and stage. We found unexpected patterns among patients with hematologic neoplasms, despite the fact that the majority of previous research assessing trends and relationships of risk with VTE have mostly focused on patients with solid tumors.

No significant role of BMI was found among the current studied groups.

The comparison of ECOG in the present study showed no significant difference, as the most frequent was 2 in both groups. There were not many patients with poor performance status in this study, so the performance status factor was not assessed properly.

Smoking among the present VTE group frequently prevailed compared to the non-VTE group, with a significant difference.

After accounting for metastasis and cancer location, smokers' risk of developing VTE in cancer patients did not alter. Since smoking worsens endothelial function and fibrinolysis and raises blood coagulability, it makes sense etiologically to anticipate that smoking will raise the risk of VTE. On the other hand, smoking was not linked to a higher incidence of VTE among participants without cancer in the current study. However, other research has shown that there is a higher incidence of VTE in smokers who are now or were previously smokers[39], in smokers who are currently smokers alone[40], and in heavy smokers alone.[41]

There was no discernible difference between the VTE and non-VTE groups according to a previous VTE history. A major risk factor for getting VTE is having had a previous episode. According to Agnelli *et al.*,[27] and Connolly *et al.*,[42] cancer patients with a history of VTE had a 6- to 7-fold higher risk of VTE recurrence than cancer patients without a history of the condition. Depending on the population under study, reported rates of CVCT range from 5% to 18%.[43] Although the VTE group in the current study had a higher prevalence of CVCT, the difference was not statistically significant.

Ellis *et al.*[44] discovered that in a sizable metropolitan Australian research involving 3130 cancer patients, CVCT occurred in 3.6% of all central VTE catheters and 4.9% of those with a PICC. According to Haggstrom *et al.*[45], there was a modest increase in thrombosis rates, which might be attributed to a higher-risk group. Specifically, 29.6% of the patients had malignancies at high risk.

The current study revealed no discernible differences between the groups under investigation with regard to treatment modes and kinds, or the existence of co-morbidities, with the exception of the chemotherapy group. As several studies have previously shown, patients who underwent systemic chemotherapy had a markedly higher chance of developing VTE.[18] Mulder *et al.*[14] found that patients receiving chemotherapy (3.35; 95% CI, 3.06-3.66), immunotherapy (3.56; 95% CI, 2.75-4.59), and targeted therapy (3.85; 95% CI, 3.43-4.32) had an elevated risk of VTE, but patients receiving endocrine therapy alone did not have a significant risk (1.18; 95% CI, 0.99-1.41). These trials[14,46] could not account for time-varying confounding from relapsed or advanced illness, and frequently included patients who

had undergone several lines of treatment. A correlation has been shown in several research between medical co-morbidities and a higher risk of thrombosis linked with malignancy. It has been discovered that patients with cancer who have comorbid conditions like renal failure, respiratory illness, heart disease, obesity, and acute infection have a higher chance of developing VTE; infection has been found to be one of the most strongly linked risk factors for VTE.[21, 25] Twenty-four percent of the VTE patients had three or more co-morbidities prior to their malignancy diagnosis, according to Mahajan *et al.*[19], compared to 17.3% of the cohort as a whole.

They all advise hospitalized patients with active cancer to receive VTE prophylaxis using one of three medication classes: factor Xa inhibitors, low-molecular-weight heparin (LMWH), or unfractionated heparin (UFH), along with graduated compression stockings or intermittent pneumatic compression when pharmacologic prophylaxis is contraindicated. The first line of therapy for VTE patients is often LMWH or UFW. It has been shown in certain trials[47,48] that there is no discernible difference in the effectiveness of UFH and LMWH. LMWH has, however, replaced Coumadin as the preferred anticoagulant in cancer patients following the historic CLOT study.[49] According to this experiment, LMWH reduced the probability of death at three months' follow-up in a statistically significant way.[49]

Although there was a decreased prevalence of non-major bleeding[50], the latest VTECH study did not demonstrate a decrease in mortality or total bleeding with LMWH compared to Coumadin. Additionally, while using LMWH as opposed to UFUH, patients had a lower risk of developing heparin-induced thrombocytopenia (HIT).[51,52] Additionally, LMWH makes the switch to outpatient care simpler. Therefore, according to Lyman *et al.*[6], LMWH is presently the preferred anticoagulant for cancer patients receiving first VTE treatment. Because of its protamine sulfate reversibility, shorter half-life, and hepatic clearance, UFH primarily plays a role in patients with severe renal impairment.

CONCLUSION

The overall incidence rate for VTE among patients with different types of tumors in Nineveh City was low. Breast CA was the most frequent tumor found among the studied groups. Stage 4 and smoking were the most critical risk factors.

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