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ORIGINAL ARTICLE

Association between Level of Tumor Markers and Development of VTE in Patients with Pancreatic, Colorectal and Ovarian Ca: Retrospective Case-Control Study in Two Community Hospitals

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Abstract The risk of venous thromboembolism (VTE) is increased in patients with cancer. However, the role of tumor markers as potential indicators of increased risk of VTE is still undetermined. In this retrospective observational case control study, levels of the tumor markers CEA, CA 19–9 and CA 125 in patients with colorectal, pancreatic, and ovarian cancer respectively, who were admitted to two community hospitals between January 2001 and December 2011, were compared between patients who were VTE positive and those who were VTE negative. The primary goal of this study was to determine whether VTE positive cancer patients had higher tumor marker levels compared to VTE negative cancer patients. In our study, 66.7% (48/72) of patients who were positive for VTE had elevated tumor markers while 65.3% (66/101) of patients who were negative for VTE had low (normal) tumor markers, indicating an association of high tumor marker levels with the diagnosis of VTE. This was statistically significant with an odds ratio of 3.77 and *p*-value of <0.0001 (95% CI of 1.99–7.14). When the VTE group was further divided into DVT and PE groups, 70.2% (40/57) of patients in the DVT positive group had high tumor markers with a *p* value of <0.0001 and an odds ratio of 3.99 (95% CI of 2.02 to 7.89) while 57.9% (11/19) of patients in pulmonary embolism positive group had high tumor markers; this was, however, not statistically significant (*p*-value of 0.35 and a CI of 0.59 to 4.10). In this retrospective study of 173 individuals with a diagnosis of either colorectal, pancreatic, or ovarian Cancer, higher tumor marker levels (CEA, CA 19–9, and CA 125 respectively) were associated with an increased risk of VTE, either DVT or PE. However, when further divided into either DVT or PE groups, the association remained statistically significant only for DVT but not for PE.

Keywords Tumor markers · Venous · Thromboembolism · Colorectal · Pancreatic · Ovarian

Background

The association between venous thromboembolism and cancer goes back in history to the nineteenth century when it was first described by Bouillaud in 1823 [1]. Over the years multiple studies have investigated the correlation between cancer and the risk of developing VTE. To date, the association between cancer and the risk of VTE whether in the form of DVT or PE has long been established.

VTE affects up to 20% of patients with cancer before death and has been reported in up to half of the cancer patient at the time of postmortem examination [2]. It is estimated that the risk of developing recurrent VTE is increased two to nine folds in patients with active cancer [3] and is the second leading cause of death in hospitalized patients [4].

Several mechanisms have been proposed to explain this association, including the release of procoagulant by the tumor, reduced fibrinolytic activity, and extrinsic venous compression by the tumor. The prothrombotic state is further enhanced by antineoplastic therapy including surgical procedures, chemotherapy, central venous catheters, and supportive care agents [4, 5].

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Sites of cancer that are associated with highest rates of VTE include the pancreas (8.1%), kidneys (5.6%), ovaries (5.6%), lungs (5.1%), and stomach (4.9%). Among the hematologic malignancies, myeloma (5%), non-Hodgkin lymphoma (4.8%), and Hodgkin disease (4.6%) were reported to have the highest rates of VTE [2, 6].

In attempts to identify risk factors that may be associated with higher risk of VTE development in cancer patients, Multiple biomarkers were studied as predictors of VTE in cancer patients such as D-dimer, sP-selectin, CRP, leukocyte count, platelet count, hemoglobin level and more. Out of these parameters, D-dimer appeared to be the most promising as a predictor of VTE in cancer patients [7].

A small number of studies looked at specific tumor markers and their correlation with VTE in cancer patients [8–10]. To our knowledge, there have been no studies that looked at multiple tumor markers collectively as biomarker predictors of VTE development in cancer patients. To our knowledge, this study is the first to investigate three different tumor markers (CEA, CA-125, and CA 19–9) and their association with the risk of VTE.

Methods

After IRB approval for Retrospective Observational case control study was obtained, patients' records that meet the inclusion criteria were reviewed. The inclusion criteria for the test group consisted of patients between the age of 21 and 99 with one of the three cancer types (pancreatic, colorectal or ovarian) who were diagnosed with VTE (DVT or PE) by ultrasound or CT angiogram respectively. Tumor marker levels for CA125, CA19–9 and CEA for ovarian, pancreatic and colorectal cancer respectively were required within six months of an event (VTE). Patients who did not meet the criteria were excluded. The control group were patients who have one of the three types of cancer without VTE proven by ultrasound and CT angiogram and again tumor markers measured within 6 months of the negative imaging results.

Medical records from January 2001 to December 2011 at St. Joseph's regional Medical and St. Michael's Medical Center were reviewed. Patients' identification characteristics were de identified by numbers as per IRB regulations.

Clinical characteristics such as age, gender, medical history (HTN, Diabetes, CAD, chronic kidney and liver disease) as well as smoking history were recorded. Imaging studies including venous ultrasound of the extremities and CT angiogram of the chest were obtained. Tumor marker levels within six months of imaging date were recorded. The normal range for CEA was 10, for CA19–9 it was 35 and for CA125 it was also 35, as per hospital laboratory guidelines.

Patients with one of the three types of cancers were grouped into VTE positive and VTE negative groups. Risk factors and demographics were determined among both groups. With outcome determined as: Does higher tumor marker level leads to VTE development?

Statistical analysis was performed using the Chi-square (and Fisher's exact) test and T test were used for baseline characteristics. P value ≤ 0.05 was considered to be statistically significant. All analyses were performed using Graphpad Prism software version 5. Results are reported with 95% confidence intervals.

Results

The present analysis includes a total of 173 patients, 101 in the control group and 72 in the VTE + group. Baseline clinical characteristics of all patients are shown in Table 1A, with no statistically significant differences (P value ≤ 0.05) noted in gender, age, smoking, or presence of CAD, HTN, diabetes or chronic kidney and/or liver disease between the VTE positive and control groups.

We collected the data for three types of cancer with associated tumor markers, these being Colon Cancer with CEA level, Pancreatic cancer with CA19–9 level and Ovarian Cancer with CA125. The number of cases in each group is illustrated in Table 2.

The primary outcome of the study was to examine tumor marker levels in cancer patients with VTE. In this study, 66.7% (48/72) patients with high tumor markers were positive for VTE while 65.3% (66/101) with low (normal) tumor

Table 1 Baseline characteristics – All cases

Characteristics	VTE+ group	VTE - Group	Missing variable	p value
Gender M/F	24/47	50/51	1	0.61
Mean Age	66.81	63.13	0	0.76
Smoking +/−	14/56	29/72	2	0.106
CAD +/−	10/61	13/87	2	0.951
Hypertension +/−	33/38	53/48	1	0.366
Diabetes Mellitus +/−	19/52	34/67	1	0.31
Chronic Kidney Disease +/−	6/65	11/90	1	0.430
Chronic liver Disease +/−	2/69	2/99	1	0.463

Table 2 Types of cancer and VTE

		VTE		Total
		Negative	Positive	
Type of Cancer	Colon Cancer	67	31	98
	Pancreatic Cancer	26	21	47
	Ovarian cancer	8	20	28
Total		101	72	173

markers were negative for VTE, thus showing an association of high tumor marker levels with the diagnosis of VTE. This was statistically significant with an odds ratio of 3.77 and *p*-value of <0.0001 (95% CI of 1.99–7.14) (Table 3).

When the VTE group was further divided into DVT and PE groups, 70.2 % (40/57) patients in the the DVT positive group had high tumor markers with a p value of < 0.0001 and an odds ratio of 3.99 (95% CI of 2.02 to 7.89). The pulmonary embolism group had a 57.9% (11/19) patients with high tumor markers with a positive pulmonary embolism; this was, however, not statistically significant (p-value of 0.35 and a CI of 0.59 to 4.10).

A subgroup of our analysis focused on each cancer with its respective tumor marker and the correlation with VTE. An unpaired-samples t-test was conducted to compare the mean tumor marker level specific to each cancer in VTE negative and VTE positive patients.

When comparing the mean CEA level between VTE negative patients with colorectal cancer (n = 66, mean = 47.20, SD = 174.2) and VTE positive patients with colorectal cancer (n = 30 mean = 155.88, SD = 312.14), there was a significant difference in mean CEA level between the two groups (difference between means = −108.67, Standard error of mean difference = 49.76, t(94) = −2.184, p < 0.001, 95% CI = −207.46 to −9.88.

When comparing the mean CA19–9 level between VTE negative patients with pancreatic cancer (n = 26, mean = 5928.15, SD = 10,985.98) and VTE positive patients with pancreatic cancer (n = 19 mean = 15,609.66, SD = 28,227.14), there was no significant difference in mean CA 19–9 level between the two groups (difference between means = −9681.51, Standard error of mean difference = 6064.19, t(43) = −1.597, p = 0.16, 95% CI = −21,911.13 to 2548.10.

When comparing the mean CA-125 level between VTE negative patients with ovarian cancer (n = 8, mean = 127.89, SD = 227.04) and VTE positive patients with ovarian cancer (n = 20 mean = 2771.04, SD = 6047.80), there was no significant difference in mean CA-125 level between the two groups (difference between means = −2643.15, Standard error of mean difference = 2163.31, t(26) = −1.222, p < 0.068, 95% CI = −7089.90 to 1803.60.

Discussion

Venous Thromboembolism is a major complication that occurs in cancer patients that can significantly affect their morbidity and mortality. Many biomarkers have been studied as predictors of VTE in patients with cancer including leukocyte count, platelet count, hemoglobin level, soluble P-selectin, D-dimer, prothrombin factor 1 + 2, tissue factor and fibrinogen, factor VIII activity and, CRP level, protein C, protein S, and homocysteine level [6, 7, 11–13].

Two risk assessment models have been published for identification of cancer patients at high risk for VTE. One risk assessment model was developed by Khoran et al. that used 5 clinical and laboratory parameters to calculate VTE risk assessment score which includes site of cancer, platelet count, hemoglobin level and/or use of erythropoiesis, leukocyte count, and BMI [11]. Another expanded risk model, the Vienna VTE Risk Assessment Score, developed by Ay et al., incorporated the same parameters that Khorana VTE risk assessment model included, in addition to sP-selectin and D-dimer to improve the risk prediction of VTE in their model [12].

To date, there are no published risk assessment models that include any of the tumors markers in their scoring systems, and there are no studies that investigated multiple tumor marker trends as independent risk factors for the development of

Table 3 Chi-square test with VTE and High tumor markers

			High tumor markers		Total
			Low tumor markers	High tumor markers	
VTE	Negative	Count	66	35	101
		% within VTE	65.3%	34.7%	100.0%
	Positive	Count	24	48	72
		% within VTE	33.3%	66.7%	100.0%
Total		Count	90	83	173
		% within VTE	52.0%	48.0%	100.0%

VTE in cancer patients. To our knowledge this is the first study to look at multiple tumor markers in the setting of different types of cancers as a possible independent risk factors for the development of VTE.

In this retrospective observational case control study, when all three tumor markers levels were looked at collectively, there was a statistically significant association between tumor marker elevation and VTE occurrence. 66.7% of patients with elevated tumor markers were positive for VTE compared to 33.3% in patients with low (normal) tumor markers. And even though DVT is generally considered a precursor of PE, and both DVT and PE are considered a spectrum of the same disease, when we divided the VTE positive patients to separate DVT positive and PE positive groups, our study showed statistically significant association between tumor marker and DVT occurrence but not PE occurrence. This can be attributed to the larger sample of patients with DVT compared to patients with PE given that the latter is less common to occur.

When our patients sample was subdivided further to each cancer and its corresponding tumor marker, CEA was the only tumor marker that showed statically significant association between level elevations and occurrence of VTE. And even though both CA19–9 and CA-125 mean levels were higher in VTE positive patients compared to VTE negative patients, both have failed to show statistically significant association between the level of elevation and the occurrence of VTE, which can also be attributed to a larger sample size of patients with colorectal cancer compared to patients with pancreatic and ovarian cancer.

There are no studies to date that studied the correlation between CEA levels in patients with colorectal cancer and the risk of VTE. One research by Zhang et al. studied the correlation between CEA level and VTE incidence in patients with lung cancer and found linear association between CEA level and the increased risk of PE that was borderline significant [8]. Our research is the first that shows that elevated CEA level in patients with colorectal cancer is associated with increased risk of VTE, and with numerous risk scoring models that include other risk factors, it is possible that now elevated CEA could also be used to assess the risk of VTE in patients with colorectal cancer.

Two studies by Abu Saadeh et al. and Wu et al. showed statistically significant correlation between CA-125 level in patients with ovarian cancer and increased risk of VTE [9, 10]. Interestingly, our study failed to show the same statistical significance which is probably related to our smaller sample size. To our knowledge, there are yet no studies that investigated the correlation between CA19–9 levels and the risk of VTE. Although our research is the first to study this correlation, it did not show statistical significance which is again most likely related to the small sample size.

We believe that it is worth to further investigate the correlation between the above mentioned tumor markers and the risk of VTE in cancer patients, and to use the results of such studies to corporate tumor marker levels, specially CEA, to the risk assessment models which can further improve outcomes and set guidelines for thromboprophylaxis for high risk patients. In addition, it would be interesting to examine the change in tumor marker levels before and after VTE development and to evaluate if sudden increase in tumor marker level puts the patient at a greater risk for VTE.

Study Limitations

First, the number of participants in the study was limited. Second our control group was determined with patients where VTE was ruled out using imaging studies in the most common sites of VTE development (Lungs and extremities) it was impossible to completely rule out the presence of a VTE in these patients in uncommon sites. Finally, tumor marker levels were not always performed at the time of VTE diagnosis, we documented all those within a 6 month period, we have to keep in mind that tumor marker levels may vary. This limits our study, but our findings warrant further investigation regarding the use of tumor marker levels in assessing the risk of VTE in cancer patients.

Conclusion

In this study, we showed for the first time that elevation of CEA in colorectal cancer patients is associated with the increased risk for VTE. Interestingly, no association was seen between CA19–9 and CA-125 elevation and VTE in those with pancreatic cancer and ovarian cancer respectively. Tumor marker elevation combined with other risk factors should be used to assess a patient's risk of developing VTE and need for thromboprophylaxis to decrease the morbidity and mortality associated with VTE in cancer patients.

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