Relation of Venous Thromboembolism Risk to Ischemic Stroke Risk in Hospitalized Patients with Cancer

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Patients with cancer are at increased risk for venous thromboembolism (VTE). However, the relationship of cancer type to the risk of arterial thrombosis in patients with high VTE risk has not been described. The goal of this study is to determine the rate of arterial thrombosis in patients with different types of solid tumors stratified by VTE risk. Using the 2012 National Inpatient Sample, we identified 373,789 hospitalizations involving patients ≥18 years associated with solid tumors, stratified by type. Data were collected on clinical characteristics, VTE (deep vein thrombosis [DVT] and pulmonary embolism [PE]), and arterial thrombosis (primary diagnosis of myocardial infarction [MI] and ischemic stroke). Subjects with solid tumors (stages I to IV) were stratified by VTE risk − high versus low. Certain solid tumor types (esophageal, lung, melanoma, ovarian, pancreatic, stomach, and uterine) were found to be associated with a higher rate of VTE compared with other cancer types (6.8% vs 3.9%, $p < 0.001$). Multivariate analysis applied to the high VTE risk group showed no increased risk for MI (odds ratio [OR] 0.93, $p = 0.74$), however, the rate of ischemic stroke was increased (OR 1.22, $p < 0.001$). Those in the high VTE risk group who had metastatic disease were at higher risk for arterial thrombosis (MI OR 1.35, $p < 0.001$, ischemic stroke OR 2.43, $p < 0.001$). In conclusion, different cancer types are associated with increased risk of both venous and arterial thrombosis and the risk is further increased by the presence of metastatic disease. **(Am J Cardiol 2019;123:679−683)**

Cardiovascular disease and cancer are the 2 leading causes of death in the United States.[1] As advances in medical therapies for both disease processes have led to prolonged survival, the 2 have become increasingly comorbid conditions.[2] Whereas the cardiotoxic effects of different chemotherapeutic agents have been well documented,[3] evidence is now emerging that the presence of cancer itself is associated with increased risk for many cardiovascular diseases.[2,4−6] The relationship between cancer and venous thromboembolism (VTE) has been well described[5,7] and is associated with increased morbidity, mortality, and cost of medical care.[5−9] More recent evidence has also identified cancer as a risk factor for arterial thrombotic events, including ischemic stroke and potentially myocardial infarction (MI).[4,10−16] Novel investigations that have demonstrated distinct pathophysiologic mechanisms of stroke in cancer patients compared with the general population suggest that ischemic stroke cannot be fully accounted for by traditional risk factors in these patients.[11,14,17,18] The role of cancer in arterial thrombosis however has not yet been fully defined and it is unclear if it is related to the increased risk for thromboembolism in the venous system. Certain cancer types have been shown to confer a higher risk for VTE than others,[5] however it is not known if this relationship extends to the arterial portion of the circulatory system. The purpose of this study is to evaluate the rate of arterial thrombosis in hospitalized patients with cancer as stratified by risk of VTE.

Methods

Data were obtained using the 2012 National Inpatient Sample (NIS), a database developed by the Healthcare Cost and Utilization Project (HCUP) in partnership with the Agency for Healthcare Research and Quality (AHRQ), comprised of an unweighted sample of 20% of discharges from participating hospitals representing 7.3 million hospitalizations. The NIS includes data from hospitals representative of more than 95% of the US population and includes all payer sources. The NIS is a collection of administrative data of discrete hospitalizations and as such does not contain information related to medications or long-term outcomes beyond the hospitalization itself. The database consists of de-identified patient data and thus institutional review board approval and informed consent were not required for this study.

Hospitalizations met inclusion criteria if the subjects were older than 18 years of age and had an active diagnosis of cancer. These were identified with the aid of clinical classifications software (CCS), a tool developed by the HCUP and AHRQ to categorize diagnoses based on administrative data in order to group ICD-9 (*International Classification of Diseases, 9th revision*) codes into

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categories reflective of clinical practice. CCS codes were utilized to identify and group patients with solid tumor malignancies (stages I to IV). Patients with a history cancer but no active diagnosis at the time of the index hospitalization were excluded from the analysis. Analysis was limited to solid tumors because classification of tumor stage utilizing administrative data is limited in hematologic malignancy.

Data were collected on clinical characteristics including patient demographics, comorbidities, and relevant risk factors including age, sex, atrial fibrillation (427.31), previous history of VTE (V12.51), congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx), hyperlipidemia (272.0, 272.1, 272.2, 272.3, 272.4), tobacco use (305.1), systemic anticoagulation (V58.61), antiplatelet therapy (V58.66, V58.63), coronary artery disease (414.0x), and calculated average CHADS2 score. Pertinent comorbidities as defined by the AHRQ were also included in the analysis. These include metastatic cancer, alcohol and drug abuse, anemia, chronic pulmonary disease, coagulopathy, diabetes, hypertension, liver disease, fluid and electrolyte disorders, obesity, peripheral vascular disease, psychiatric disorders, renal failure, valve disease, and weight loss. These comorbidities have been validated in previous studies utilizing administrative data sets as predictors of mortality, length of stay, and cost. For a full list of ICD-9 codes used in this study, please see the associated supplement.

The primary outcomes investigated were deep vein thrombosis (453.0, 453.4x, 453.8x [excluding 453.81]), pulmonary embolism (PE; 415.xx), myocardial infarction (410.xx), and ischemic stroke (433.x1, 434.x1). Myocardial infarction and ischemic stroke were included as an outcome only if it was the primary diagnosis for the hospitalization.

A VTE rate was calculated for each tumor type to stratify cancers by VTE risk. The VTE rate was calculated by identifying the number of patients with a cancer type that also had a diagnosis of either DVT or PE, divided by the total number of patients with that cancer. Chi squared analysis was undertaken to evaluate the VTE rate for each tumor type against the rate of the overall cohort. Cancer types with a VTE rate that was statistically elevated ($p < 0.05$) relative to the VTE rate of all other cancers was grouped into an elevated VTE rate cohort whereas cancers with a VTE rate statistically insignificant from the remaining cohort were also grouped for comparison.

Further subgroups were created to evaluate the contribution of disease burden to VTE risk and arterial thrombosis. Patients were stratified into metastatic disease and non-metastatic disease groups and a subgroup of patients in the elevated VTE rate cohort with metastatic disease were also analyzed against the rest of the data set.

Multivariate logistic regression was performed using comorbidity variables included in the dataset as well as those extracted from diagnostic codes to evaluate the contribution of VTE rate as well as the presence of metastatic disease to primary outcomes. Pearson's chi-square was used to evaluate dichotomous variables and the Welch's *t* test was used to evaluate continuous variables. Multivariate logistic regression was performed using comorbidity variables as defined by the AHRQ and those extracted from diagnostic codes to evaluate the contribution of cancer to primary outcomes. Statistical analyses were performed with STATA IC/13.0 software. Associations were considered statistically significant for p value <0.001.

Results

A total of 354,347 patients with active solid tumor cancer diagnoses were hospitalized between January 1, 2012 and December 31, 2012. The solid tumor types with the highest rates of DVT were pancreatic (6.5%), testicular (5.1%), ovarian (4.7%), gastric (4.4%), uterine (4.0%), esophageal (4.0%), and lung (3.9%). Similarly, pancreatic cancer had the highest rate of PE (4.5%), followed by lung (3.9%), ovarian (3.4%), testicular (3.4%), esophageal (3.1%), uterine (3.0%), and gastric (2.8%) (Figure 1). The rates of VTE, as determined by the combined rate of DVT or PE, were significantly elevated in these 7 cancer types compared with others (6.8% vs 3.9%, p <0.001), and were therefore grouped into the elevated VTE rate cohort. This subgroup represented 37.8% (n = 134,001) of the total cohort. The rest of the cancer types comprised the standard VTE rate cohort.

Clinical characteristics for the 2 cohorts are described in Table 1. The elevated VTE rate group were significantly

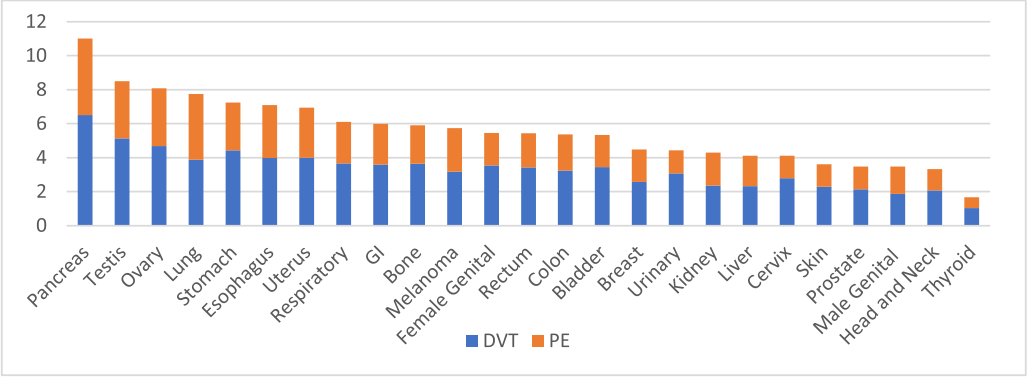

Figure 1. VTE rate by cancer type. The above graph depicts the rates of VTE, as represented by combined DVT and PE rates, for each cancer type. The cancers that comprise the elevated VTE rate cohort are shown at the far left of the graph and include cancer of the pancreas, stomach, ovary, testis, esophagus, lung, and uterus, with VTE rates of 11.0%, 8.5%, 8.1%, 7.7%, 7.3%, 7.1%, and 7.0%, respectively.

Table 1
Characteristics of standard VTE rate cancers and elevated VTE rate cancers

Characteristic	Standard VTE rate cancers	Elevated VTE rate cancers	p Value
Number of patients	220346 (62.2%)	134001 (37.8%)	
Age (years, mean)	64.9	67.0	p <0.001
Female	47.0%	54.1%	p <0.001
Hypertension	51.9%	54.9%	p <0.001
Hyperlipidemia	28.0%	30.6%	p = 0.19
Atrial Fibrillation	11.0%	14.6%	p <0.001
Congestive Heart Failure	9.5%	10.6%	p <0.001
Diabetes Mellitus	22.2%	24.3%	p <0.001
Peripheral Vascular Disease	4.8%	6.8%	p <0.001
Prior Stroke or TIA	1.5%	1.5%	p = 0.94
Coronary Artery Disease	15.9%	18.4%	p <0.001
Renal Failure	11.0%	9.0%	p <0.001
Tobacco Use	10.9%	17.3%	p <0.001
Systemic Anticoagulation	4.5%	5.5%	p <0.001
Antiplatelet Therapy	6.1%	6.4%	p = 0.004
Metastatic Disease	25.3%	30.2%	p <0.001
CHADS2 Average	1.1	1.2	p <0.001

(p <0.001) older (67.1 vs 64.1), female (54.1% vs 47.0%), and more likely to have a history of tobacco use (17.3% vs 10.9%). This group also had a greater burden of cardiovascular comorbidities, with higher rates of hypertension (54.9% vs 51.9%), atrial fibrillation (14.6% vs 11.0%), congestive heart failure (10.6% vs 9.5%), diabetes (24.3% vs 22.2%), peripheral vascular disease (6.8% vs 4.8%), and coronary artery disease (18.4% vs 15.9%). The elevated VTE rate group had a slightly higher calculated average CHADS2 score (1.19 vs 1.13) and was more likely to be on a systemic anticoagulant (5.5% vs 4.5%). Additionally, the elevated VTE rate group had a higher rate of previous VTE (5.1% vs 3.8%) and metastatic disease than the standard VTE risk group (30.2% vs 25.3%). The 2 groups did not significantly differ in rates of hyperlipidemia or history of stroke/TIA.

The unadjusted rates for the 2 primary outcomes of interest, myocardial infarction, and ischemic stroke, reveal that patients in the elevated VTE rate group and the standard VTE rate group were equally likely to experience a myocardial infarction (6.8% vs 6.7%, p = 0.60). However, patients with elevated VTE rate cancers were more likely to suffer an ischemic stroke (0.76% vs 0.62%, p < 0.001).

The results of the multivariate analysis are shown in Table 2. When controlling for multiple comorbidities, elevated VTE rate cancers were significantly associated with ischemic stroke (odds ratio [OR] 1.22, p < 0.001) but not with myocardial infarction (OR 0.93). The presence of metastatic disease, however, increased the likelihood for both ischemic stroke (OR 1.80, p < 0.001) and MI (OR 1.31, p <0.001). Furthermore, those in the elevated VTE rate group that also had metastatic disease were at highest risk for stroke (OR 2.43, <0.001) and MI (OR 1.35, p < 0.001) when compared with the rest of the cohort. When the presence of atrial fibrillation was excluded from the analysis, the observed relationship between VTE and arterial thrombosis was further strengthened.

Discussion

To our knowledge, this is the first study to describe an association between VTE and arterial thrombosis in patients with different types of solid tumor cancers. Our analysis reveals that certain cancers with high rates of VTE (pancreatic, testicular, ovarian, lung, gastric, esophageal, and uterine) are associated with increased risk for ischemic stroke. This risk is further augmented by the presence of metastatic disease. These findings suggest that a positive relationship exists between the risk of VTE and arterial thrombosis and that this relationship is more significant with increasing extent of disease.

The results from our multivariate analysis support the hypothesis that ischemic stroke in patients with cancer is related to factors that similarly predispose individuals to VTE. Previous research has shown an increase in arterial thrombosis following a diagnosis of VTE, and vice versa.[19,20] Arterial events, including embolic stroke in atrial fibrillation, may also be influenced by the same factors that provoke VTE. The presence of cancer has been shown to result in an imbalance of the hemostatic system and

Table 2
Multivariate analysis for patients with elevated VTE rate cancers, metastatic disease, and both elevated VTE rate cancers and metastatic disease combined

	Myocardial infarction		Ischemic stroke	
	OR	CI	OR	CI
Elevated VTE Rate Cancers	0.93	0.85-1.02	1.22	1.12-1.33
Metastatic Disease	1.31	1.19-1.43	1.80	1.66-1.97
Elevated VTE Rate Cancers + Metastatic Disease	1.35	1.20-1.52	2.43	2.43-2.69

proposed mechanisms that may explain this phenomenon include the induction of a state of generalized inflammation by cancer cells, activation of normal host cells to transition to a procoagulant phenotype, and overexpression of procoagulant proteins and adhesion molecules by tumor cells.[21]

Our results are consistent with other studies that have shown that tumor-related factors such as primary site and stage of cancer are important risk factors for the development of VTE in cancer patients.[5,22–25] Multiple large cohort studies have corroborated our findings that the malignancies most often associated with VTE include pancreatic, upper gastrointestinal, gynecological, and lung cancers.[5,22–25] Similarly, these studies support our findings in providing strong evidence that patients with metastatic cancer are at higher risk for VTE compared with patients with localized cancer.[5,9,22–25,26]

The use of administrative data provides both strengths and limitations in this study. The large sample size and extensive information available in the NIS allows for robust statistical comparisons and evaluations across many patient subtypes, and confers a degree of generalizability lacking in smaller studies. The inclusion of data from all payer sources across hospitals nationwide reduces bias in patient selection. The limitations of administrative data are well known and have been widely described in the literature. Administrative data are not as reliable as clinical data and do not provide complete information regarding individualized treatment. More specifically information regarding medication use is likely underreported in most administrative datasets which may affect the conclusions that can be drawn regarding management decisions. The NIS in particular does not provide longitudinal data, limiting our findings to in-hospital events only. Whereas previous research on the accuracy of administrative data for myocardial infarctions and ischemic stroke has found it to have high sensitivity, positive predictive value, and clinical accuracy, we consider our analysis to be hypothesis-generating and suggests the need for high quality work on the key questions regarding cancer and cardiovascular disease.[27,28]

Despite these considerations, our data demonstrate that certain cancer types are associated with increased risk of both VTE and arterial thrombosis. Current guidelines fall short of capturing the clinical complexity of many of these patients with cancer and do not address questions involving the relationship between cancer, VTE, and arterial thrombosis.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.008.

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