The Impact of Venous Thromboembolism on Risk of Death or Hemorrhage in Older Cancer Patients

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BACKGROUND: Among older cancer patients, there is uncertainty about the degree to which venous thromboembolism (VTE) and its treatment increase the risk of death or major hemorrhage.

OBJECTIVE: To determine the prevalence of VTE in a cohort of older cancer patients, as well as the degree to which VTE increased the risk of death or major hemorrhage.

METHODS: We conducted a retrospective cohort study of linked Surveillance, Epidemiology, and End Results cancer registry and Medicare administrative claims data. Patients with any of ten invasive cancers diagnosed during 1995 through 1999 were included; the independent variable was VTE diagnosed concomitantly with cancer diagnosis. Outcomes included major hemorrhage during the first year after cancer diagnosis and all-cause mortality;

RESULTS: Overall, about 1% of patients who were diagnosed with cancer also had a VTE diagnosed concomitantly. After adjusting for sociodemographic factors and cancer stage and grade, concomitant VTE was associated with a relative increase in the risk of death for 8 of the 10 cancer types; the increase in risk tended to range 20–40% across most cancer types. Approximately 16.8% (95% confidence interval [CI] 14.9–18.8%) of patients with a concomitant VTE and 7.9% (95% CI 7.7–8.0%) of patients without a VTE experienced a major hemorrhage during the year after cancer diagnosis (*P* value <.001). The excess risk of hemorrhage associated with VTE varied substantially across cancer types, ranging from no significant excess (kidney and uterine cancer) to 11.5% (lymphoma).

CONCLUSION: Concomitant VTE is not only a marker and potential mediator of increased risk of death among older cancer patients, but patients with a VTE have a marked increased risk of major hemorrhage.

BACKGROUND

Increasing age and cancer are well-established risk factors for venous thromboembolism (VTE).[1–6] Given that older persons bear most of the cancer burden, as the population ages the incidence of cancer-associated VTEs will increase as well.[7,8] However, the epidemiology of VTE in older cancer patients has not been well described. Prior efforts have largely focused on either hospitalized patients or were not able to collect longitudinal data on a sufficient number of patients.[1,9,10] As a result, we lack information about the degree to which VTE increases the risk of death or anticoagulation-associated complications such as hemorrhage at the population level.

Prior work has suggested that cancer patients with a VTE have a two- or threefold greater risk of death.[3,11] If a VTE diagnosis truly does independently increase the risk of death threefold, it would have profound implications for prognostication, management, and prophylaxis of VTE in cancer patients. It is also possible that the impact of VTE on mortality may be less pronounced than prior studies have suggested because VTEs are associated with more aggressive tumor characteristics and later stage at diagnosis.[10] Prior studies have not fully accounted for patient and tumor factors and it is unclear to what degree VTEs are truly a risk factor for mortality or if they are simply a marker of more aggressive tumors.[11] Furthermore, given that cancers vary in the degree to which they are associated with thrombosis, it could be expected that the impact of VTE on subsequent survival could vary across cancer types.[12] Information about whether VTE is associated with increased risk of death for different types of cancer could inform decision-makers about the intensity and duration of VTE prophylaxis and treatment.

Hemorrhage is a major concern when treating VTE patients with anticoagulant therapy. Although some work has suggested that patients with a VTE could benefit from prolonged or even indefinite anticoagulation, the hemorrhage risks for patients with VTE are uncertain.[13,14] While the frequency of major hemorrhage reported in clinical trials was quite low, recent analyses of anticoagulation treatment of both cancer and noncancer patients in the community setting have suggested that major bleeding rates were up to tenfold higher.[4,15,16] Moreover, subgroup analyses suggested that patients with VTE in the setting of cancer may have a higher hemorrhage risk than patients with VTE alone.[4,15,16] In addition, patients with some types of malignancies may be more prone to major hemorrhage than others because of anatomic location or disordered hemostasis associated with the underlying

malignancy.[17] As a result of these areas of uncertainty, there has been a call for population-based data documenting the rate of hemorrhage among cancer patients with VTE.[18]

To address these knowledge gaps, we conducted a longitudinal population-based study of older cancer patients to determine how frequently VTE is diagnosed concomitantly with cancer and the degree to which VTEs increase the risk of death or major hemorrhage for different types of cancer.

METHODS

Data Sources and Study Sample

We obtained data on patients diagnosed with cancer during 1995 through 1999 from the linked National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER)–Medicare database. All incident cancer patients who reported to the SEER registries are cross-matched with a master file of Medicare enrollment.[19,20] Patient level information available includes sociodemographic characteristics, cancer type, grade, site, and stage.[21]

We identified all patients who were diagnosed with 1 of 10 common cancer types, selected on the basis of their high overall incidence rates as well as prior studies demonstrating a relationship with VTE.[11,12] To allow for a 2-year ascertainment period for previous VTE as well as other comorbid conditions before their cancer diagnosis (see below), we only included patients who were 67 years of age and older at the time of their cancer diagnosis.

Table 1 demonstrates the construction of the study sample. Of a total of 410,315 patients in the database, we included only the 247,785 individuals who were 67 years of age or older at the time of diagnosis, had a malignant primary lesion diagnosed during 1995 through 1999, and had a known cancer type and month of diagnosis. Exclusions included date of death before cancer diagnosis (23 patients), ineligible for Medicare Part A or Part B (17,477), and enrollment in a managed care plan during a 2-year period before cancer diagnosis (60,771). These latter groups of patients were excluded because claims from these beneficiaries were not included in Medicare claim files. Patients who dropped coverage and/or enrolled in a managed care plan after their cancer diagnosis were censored at the month the fee-for-service coverage terminated. Finally, we restricted our study sample to patients who had no diagnosis of VTE (defined as the absence of any ICD-9 codes) between 6 and 24 months before their cancer diagnosis to increase the likelihood that patients defined as having a "concomitant" VTE did not have a prior VTE.

Construction of Variables

A VTE was defined as the diagnosis of either deep venous thrombosis (DVT) or pulmonary embolism (PE). Cases were ascertained through hospital admissions associated with specific *International Classification of Diseases*, 9th revision, Clinical Modification (ICD-9-CM) codes. The relevant ICD-9-CM codes used for the diagnosis of DVT or PE were 451.1, 451.11, 451.19, 453.2, 451.81, 453.2, 453.3, 453.8, 453.9, 415.1, 415.11, and 415.19. We included only VTEs for which we could identify a specific hospital admission. We defined a VTE as presenting concomitantly with a cancer diagnosis if the VTE diagnosis was made between 6 months prior and 1 month after

the initial cancer diagnosis. The 6-month prediagnosis window was selected because many cancer-related VTEs may be diagnosed before recognition of the underlying malignancy.[3,22,23]

We defined major hemorrhage as an intracranial or gastrointestinal hemorrhage requiring hospital admission. The ICD-9-CM codes for intracranial hemorrhage—codes 430, 431, or 432—were derived from validated work using administrative claims data.[24] Similarly, ICD-9-CM codes for gastrointestinal hemorrhage (456.0x, 530.7, 530.82, 531–5, 537.83, 562.02–03, 562.12–13, 569.3, 569.85, and 578.xx) were also derived from previously published approaches.[25]

Cancer stage was determined using SEER American Joint Committee on Cancer (AJCC) stage or "historical stage" (coded as local, regional, or distant) for cancer types in which AJCC was not available (lymphoma, pancreatic, renal, and prostate cancers). We used median income according to patient ZIP code of residence as a proxy for socioeconomic status (SES). Dichotomous cancer treatment variables were created using SEER data and Medicare claims to identify patients who had received cancer-specific surgery, chemotherapy, and radiation therapy.[26,27]

Pertinent "comorbidity" diagnosis codes during the period before each patient's cancer diagnosis were obtained from the inpatient and outpatient claims to identify conditions that comprise the Charlson comorbidity index.[28] We only included conditions that appeared on either one inpatient or two outpatient claims.[28] To enable us to capture additional conditions that could alter the risk of developing a VTE, we also identified patients with a diagnosis code for atrial fibrillation (ICD-9 code 427.3) prosthetic heart valve (ICD-9 code 35.20, 35.22, 35.24, 35.26, or 3528), obesity (278.x), hip fracture (ICD-9 code 352.0, 352.2, 352.4, 352.6, or 352.8), or insertion of a central venous catheter (CPT code 36533) during the 2-year period before their cancer diagnosis.

Statistical Analysis

To understand the degree to which the relation between VTE and mortality is mediated by cancer-related and other factors, we constructed a series of sequential models for each cancer type. The initial Cox proportional hazards model incorporated

Table 1. Construction of Study Sample

	Number of patients	Percentage
Total patients	410,315	100.0
Exclusions		
Not malignant primary	30,450	7.6
First cancer diagnosis outside of 1995–1999	40,207	10.0
Age <67	111,142	27.7
Cancer type not of interest	12,241	3.1
Unknown month of cancer diagnosis	2,051	0.5
Eligible	247,785	61.7
Additional exclusions		
Date of death before cancer diagnosis	23	0.0
Not eligible for Part A or Part B during 2-year period before cancer diagnosis	17,477	7.1
HMO enrollment during 2-year period before cancer diagnosis	60,771	24.5
Prior claim for VTE	3,632	0.9
Study sample	167,385	40.8

VTE=venous thromboembolism.

Table 2. Concomitant Venous Thromboembolism (VTE) According to Cancer Type

Cancer type	Number of patients	Concomitant VTE (occurring 6 months before to 1 month after cancer diagnosis)	
		N	%
Prostate	40,710	152	0.37
Breast	26,563	102	0.38
Bladder	11,063	79	0.71
Uterus	5,685	71	1.25
Lung	32,348	449	1.39
Colorectal	29,101	453	1.56
Lymphoma	8,022	145	1.81
Pancreas	6,393	139	2.17
Kidney	4,141	103	2.49
Ovary	3,359	92	2.74
Total	167,385	1,785	1.07

only age (by 5-year age group because of the nonlinear relation between age and mortality), race, and gender as covariates, with VTE as the independent variable and death as the outcome. We then added cancer characteristics and therapy to the model, including stage at diagnosis, histological grade, chemotherapy, radiation, and cancer-specific surgery. Because comorbid conditions could affect the probability of receiving treatment or of developing a VTE, comorbidity was then added to the model. While SES would not be expected to alter the physiologic impact of a VTE, we considered lower SES as a potential mediator of stage and comorbidity. Further, lower SES could be associated with decreased access to appropriate anticoagulation care. Hence, a final model was constructed, which included SES.

We calculated the proportion of patients who had a major hemorrhage during the first year after cancer diagnosis for each cancer type according to VTE status. The excess hemorrhage risk in VTE patients was estimated by deriving the absolute difference in hemorrhage rates between the VTE and non-VTE groups. Rates were compared using two-tailed Fischer's exact tests. Finally, we explored the potential role of hemorrhage in mediating the relationship between VTE and mortality by adding hemorrhage as a covariate to the final multivariate model.

RESULTS

The median age of patients in the study sample was 75 years (interquartile range 71, 81 years). Approximately 48% of patients were women and 87.4% were white. Overall, about 1% of the patients was diagnosed with a VTE concomitantly with their cancer diagnosis (Table 2). The cancer types that were most frequently associated with VTE were ovarian, kidney, and pancreatic (2.7%, 2.5%, and 2.2%, respectively). Conversely, breast (0.4%) and prostate (0.4%) cancers were rarely associated with concomitant VTE. In the bivariate (unadjusted) analysis, concomitant VTE was strongly associated with mortality for patients with all types of cancer (Table 3). The hazard ratio (HR) for the risk of mortality in patients with a concomitant VTE compared with those without a VTE ranged from 1.30 (95% confidence interval [CI] 1.18–1.44) among patients with lung cancer to a high of 3.06 for patients with cancer of the uterus (95% CI 2.32–4.04).

Mortality. After accounting for demographic factors, cancer characteristics, and comorbidity, the relation between concomitant VTE and mortality was attenuated substantially for patients with cancer of the breast or prostate. For example, among patients with breast cancer, the unadjusted HR associated with VTE was 2.30 (95% CI 1.76–3.01). After adjusting for age and gender, the HR decreased to 1.95 (95% CI 1.48–2.55) (Table 3). After accounting for cancer charac-

Table 3. Concomitant Venous Thromboembolism (VTE) and Risk of Death According to Cancer Type

Cancer type	Hazard of death associated with VTE (vs no VTE)									
	Model A: unadjusted		Model B: adjusted for age, sex, race		Model C: adjusted for factors in Model B + cancer characteristics and treatment		Model D: adjusted for factors in Model C + comorbidity		Model E: adjusted for factors in Model D + socioeconomic status	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Prostate	2.24	1.78–2.81	1.81	1.44–2.27	1.44	1.14–1.81	1.20	0.95–1.51	1.21	0.96–1.52
Breast	2.30	1.76–3.01	1.95	1.48–2.55	1.11	0.84–1.45	1.01	0.77–1.32	1.01	0.77–1.33
Bladder	2.80	2.17–3.62	2.84	2.20–3.66	1.57	1.21–2.03	1.54	1.19–2.00	1.43	1.13–1.80
Uterus	3.06	2.32–4.04	3.47	2.63–4.59	2.08	1.57–2.75	1.98	1.48–2.64	1.96	1.47–2.62
Lung	1.30	1.18–1.44	1.32	1.20–1.45	1.20	1.09–11.1	1.15	1.04–1.27	1.16	1.05–1.27
Colorectal	1.33	1.18–1.49	1.32	1.17–1.48	1.24	1.10–1.39	1.19	1.06–1.33	1.19	1.06–1.34
Lymphoma	1.95	1.62–2.34	1.82	1.52–2.19	1.78	1.48–2.14	1.62	1.35–1.96	1.63	1.35–1.97
Pancreas	1.31	1.10–1.55	1.35	1.14–1.60	1.28	1.08–1.52	1.26	1.06–1.49	1.26	1.06–1.49
Kidney	1.49	1.19–1.88	1.61	1.28–2.02	1.49	1.18–1.88	1.41	1.12–1.78	1.43	1.13–1.80
Ovary	1.27	1.00–1.61	1.16	0.91–1.47	1.35	1.07–1.72	1.32	1.04–1.68	1.32	1.03–1.68

Each row represents a unique model, as patients with each type of cancer were analyzed separately. Hazard ratio represents the hazard of death for patients with a concomitant VTE compared to patients with the same cancer type, but without a concomitant VTE. Cancer characteristics include stage at diagnosis and histologic grade.
CI=confidence interval.

Table 4. Concomitant Venous Thromboembolism (VTE) and Major Hemorrhage During the First Year After Cancer Diagnosis According to Cancer Type

Cancer type	Concomitant VTE		No concomitant VTE		Excess hemorrhage rate in VTE patients (%)	P value*
	N	% hemorrhage	*N*	% hemorrhage		
Prostate	129	8.5	38,371	3.6	4.9	0.007
Breast	80	10.0	24,822	3.1	6.9	0.0035
Bladder	68	13.2	10,327	5.3	7.9	0.001
Uterus	54	1.9	5,248	4.4	−2.5	0.36
Lung	382	12.6	26,897	8.1	4.5	0.003
Colorectal	388	25.8	25,836	17.9	7.9	<0.001
Lymphoma	131	22.1	6,936	10.6	11.5	<0.001
Pancreas	115	24.3	4,836	16.4	7.9	0.020
Kidney	95	10.5	3,612	8.4	2.1	0.45
Ovary	82	14.6	2,773	8.0	6.6	0.033
Total	1,524	16.8	149,658	7.9	8.9	<0.001

Concomitant VTE: VTE diagnosed between 6 months before and 1 month after cancer diagnosis. Major Hemorrhage defined as intracranial or gastrointestinal bleeding requiring hospitalization.
**P value with two-sided Fisher's exact test for difference in hemorrhage rate between patients with VTE versus without VTE for each cancer type.*

teristics and anticancer treatment received, the HR decreased to 1.11 and was no longer statistically significant (95% CI 0.84–1.45). Finally, after accounting for SES and comorbidity, the HR was 1.01 (95% CI 0.77–1.33). A similar trend was noted among patients with prostate cancer, in that in the unadjusted HR associated with VTE was 2.24 (95% CI 1.78–2.81); the HR decreased sequentially after adjusting for demographics (HR 1.81, 95% CI 1.44–2.27), cancer characteristics and treatment (HR 1.44, 95% CI 1.14–1.81), and finally SES and comorbidity (HR 1.21, 95% CI 0.96–1.52).

Unlike breast and prostate cancers, concomitant VTE was significantly associated with mortality for patients with the other eight cancer types, even after adjusting for patient and cancer factors (Table 3). The HRs associated with VTE ranged from 1.16 (95% CI 1.05–1.27) for patients with lung cancer to 1.96 (95% CI 1.47–2.62) for patients with cancer of the uterus. When we added hemorrhage as a covariate to the analysis, there was little change in the HRs associated with VTE for any of the cancer types (data not shown).

Hemorrhage. Approximately 16.8% (95% CI 14.9–18.8) of patients with a concomitant VTE were admitted to the hospital with a major hemorrhage during the year after their cancer diagnosis. In contrast, 7.9% (95% CI 7.7–8.0) of patients without a VTE experienced a hemorrhage-related admission. The excess risk of hemorrhage in VTE patients was 8.9% (95% CI 7.0, 10.8; *P* value for difference <.001). A concomitant VTE was associated with a significantly higher hemorrhage risk for patients with 8 of the 10 cancer types studied (Table 4). There was substantial variation across cancer types with regard to both baseline hemorrhage risk (i.e., proportion of patients with no VTE who had a hemorrhage) and the excess hemorrhage rate associated with VTE.

The excess risk of hemorrhage associated with concomitant VTE (and the related anticoagulation therapy) was approximately 6–8% for most cancer types. Among patients with bladder cancer, for instance, approximately 13.2% of those who had a concomitant VTE suffered a major hemorrhage, in comparison to only 5.3% of patients without a concomitant VTE, yielding an excess hemorrhage rate of 7.9%. The

attributable risk for hemorrhage associated with VTE ranged from no significant excess (kidney and uterine cancer) hemorrhage risk to 11.5% (lymphoma).

DISCUSSION

In a population-based cohort of older patients with cancer, we found concomitant VTEs were associated with increased risk of death as well as major hemorrhage for patients with most types of cancer. The 9% absolute increase in hemorrhage rate associated with VTE suggests that treatment of VTE is associated with substantial risk. The risk of death associated with VTE did not change substantively after adding hemorrhage to the multivariate model, suggesting that hemorrhage is not the mechanism through which VTE increases the risk of death. This finding should not be misinterpreted as minimizing the importance of hemorrhage. A major hemorrhage leading to hospitalization is costly, frightening, and can be associated with substantial morbidity among patients with a relatively short life expectancy.

Our analysis builds upon these studies by providing quantitative, population-based estimates of hemorrhage risk in the older cancer population. In one analysis of 181 cancer patients with VTE, the 12-month cumulative incidence of major bleeding was 12.4% (95% CI 6.5–18.2).[4] Of note, the same analysis also investigated the hemorrhage rate in VTE patients without cancer and found that it was only 4.9% (95% CI 2.5–7.4).[4] Similarly, a review of more than 2,000 patients with VTE, with and without cancer, demonstrated a bleeding-related hospitalization rate of 11.4 to 14.9 per 100 patient-years, and that patients with cancer had a higher hemorrhage risk.[15] These hemorrhage rates are substantially higher than the rate (1.1 events/100 person-years) reported in a recent meta-analysis of anticoagulation trials, which included patients with and without cancer, across a spectrum of age groups.[16] This discrepancy between trial and community outcomes is likely because of differences in study populations, monitoring of therapy, and the fact that many of the trials have included patients with and without cancer.[16,29]

A previously validated tool for assessing hemorrhage risk is the Outpatient Bleeding Risk Index, which includes risk factors such as age greater than 65 years, prior gastrointestinal hemorrhage, and specific comorbid conditions including atrial fibrillation stroke, anemia, prior myocardial infarction, or renal insufficiency.[18,30] In the context of prior work showing that cancer increases the risk of hemorrhage, and our finding that hemorrhage risk can vary substantially across cancer types, future work should seek to identify bleeding prediction tools for validation in cancer patients.

Our findings suggest that prior estimates of the relation between VTE and mortality may have been inaccurate because of confounding by tumor characteristics.[1] In one case control study of cancer patients that accounted for age, gender, and cancer type, patients with a VTE had a HR for mortality of 2.20 (95% CI 2.05–2.45).[3] Although patients with a VTE were significantly more likely to have metastatic disease than patients without a VTE, cancer stage was not accounted for in this analysis. In contrast, we found that the impact of VTE on mortality was attenuated after accounting for these factors in patients with breast or prostate cancer. This suggests that a substantial portion of the increased mortality risk previously attributed to VTE for patients with these cancer types may actually be attributed to underlying tumor characteristics and stage at presentation. Because they are common malignancies and are frequently diagnosed at an early stage, inadequate adjustment for cancer type and stage can lead to biased assessments of VTE outcomes.

There are several considerations to note in the interpretation of this study. Although other authors have used ICD-9 codes to identify patients with diagnosed VTE, and some studies have reported that this is a relatively accurate approach, many cases of VTE may not be clinically recognized, and some clinically recognized cases may not be appropriately coded.[1,23,31–33] We focused on VTEs that were diagnosed with an associated hospital admission to increase the likelihood that the VTEs were acute. However, because it is unclear whether administrative data can reliably capture the clinical diagnosis of VTE, future work should use alternate data sources to assess outcomes associated with VTE. Similarly, other comorbid conditions may not be reliably captured using administrative claims.

While there has been a trend toward increased treatment of VTEs in the outpatient setting, low molecular weight heparin was not approved for outpatient VTE treatment until December 31, 1998—near the end of our study period.[34] Our study included only older persons, so it is unclear whether our findings would generalize to a younger cancer patient population. Finally, because pharmacologic and laboratory data were not available, we were unable to identify anticoagulation management patterns for patients with VTE. Further work should identify the degree to which the substantial hemorrhage rate noted in our sample is attributable to appropriateness of therapeutic monitoring, or the interaction of anticoagulation risks with specific cancer characteristics or other comorbid illnesses. Finally, we repeated the analysis after excluding patients who were diagnosed in 1999, as low molecular weight heparin was available during this time and outpatient treatment would have affected the analysis. We found no substantive change in the adjusted hazard of death associated with VTE after excluding patients diagnosed in 1999.

Our findings shed new light on the scope and impact of VTE on older cancer patients. The substantial risk of hospitalization with a major hemorrhage in the first year after diagnosis of a VTE emphasizes the importance of identifying opportunities for risk reduction in this population. We also found that although VTE is associated with increased risk of death, this risk varied across cancer types and was, in many cases, attenuated by adjusting for underlying tumor characteristics. With the number of newly diagnosed cancer patients and cancer survivors increasing dramatically, it is imperative to further clarify the optimal approach to older cancer patients who are at risk for VTE and those who have already experienced a VTE.

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