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Predictors of Interventional Treatment Use for Venous Thromboembolism in Cancer Patients

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Abstract

Venous thromboembolic disease is a major cause of morbidity in cancer patients. The Perspective database was used to identify patients with solid tumors and a diagnosis of VTE from 2006–2012. We examined use of IVC filters, thrombolysis, and thrombectomy. Among 32,545 patients, 23.1% received an IVC filter, 1.9% thrombolytic therapy and 0.4% underwent thrombectomy. Use of IVC filters decreased between 2006 and 2012 (23.4% to 21.2%, $P=0.012$). Older patients, uninsured patients, Hispanics and those with more comorbidities were more likely to undergo filter placement while patients at rural hospitals were less likely to receive an IVC filter ($P<0.05$ for all).

Keywords

Venous thromboembolism; Inferior vena cava filter; Thrombectomy; Thrombolysis

Introduction

Venous thromboembolism (VTE), which includes deep venous thromboembolism (DVT) and pulmonary embolism (PE), is a common medical condition that affects an estimated 300,000 to 600,000 individuals in the United States annually.¹ VTE is associated with increased morbidity and mortality, with as many as 25% of PE patients experiencing acute death in some scenarios.¹ Risk factors for VTE include advanced age, hormonal contraceptive use, pregnancy, trauma, hospitalization, cancer, and surgery.² An estimated 18% of new VTEs can be attributed to a malignant neoplasm.³ VTE is a major cause of morbidity and mortality in cancer patients.

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Cancer patients have a 7-fold increased risk of VTE compared to the general population, while fatal PE is three times more likely to occur in cancer patients than in non-cancer patients.⁴ High mortality rates have been found in several population-based cohort studies of cancer patients.^{5,6} Further, the health care costs associated with VTE in cancer patients are substantial. Cancer patients who experience VTE are hospitalized at a rate 3-times higher and incur a total health care cost almost double that of cancer patients without VTE (\$74,959 compared to \$42,691, per patient).⁷

The increased burden from VTE in cancer patients is due to a combination of the complications that arise during and after VTE treatment. Cancer patients have an increased risk of bleeding during initial VTE treatment and a higher risk of developing post-thrombotic complications.^{8–10} The American College of Chest Physicians (ACCP) provides detailed guidelines for the treatment of VTE in groups of patients who are at the highest risk for VTE and associated complications. Multiple organizations, including The National Comprehensive Cancer Network, have also released guidelines for VTE treatment in cancer patients.^{11–14} Standard treatment for VTE begins with prolonged low molecular-weight heparin (LMWH), a pharmacologic anticoagulant, for as long as the cancer is active.¹⁵

In selected circumstances, inferior vena cava (IVC) filters, thrombolytic therapy, and thrombectomy are used for the treatment of VTE. IVC filters are utilized in patients who have either failed pharmacologic anticoagulation or in whom anticoagulant therapy is contraindicated, usually because of a high risk of bleeding. Thrombolytic therapy can reduce post-thrombotic complications, but is associated with a higher risk of bleeding complications.¹⁶ Venous thrombectomy is usually limited to situations in which other thrombolytic therapies are contraindicated.¹⁷ The safety and benefit of thrombectomy on a population level is not well established in cancer patients. Concern for all three of these treatments stems from the potential overuse and additional costs when indications are often uncertain. In this study, we sought to examine utilization of IVC filter placement, thrombolysis, and thrombectomy in solid tumor patients with VTE.

Methods

Data Source

The sample for study was obtained from the Perspective database (Premier, Charlotte NC). Perspective was developed to measure quality of care and resource utilization, and as of 2012, contained data from more than 500 hospitals from across the United States.^{18,19} Perspective provides information on patient demographics, clinical diagnoses and procedures, and all services billed to a patient during a hospital stay.^{18,19} Institutional review board (IRB) exemption was obtained from Columbia University.

Patient Selection

We identified individuals 18 years of age or older with a diagnosis of venous thromboembolism (VTE) based on International Classification of Disease, Ninth Revision (ICD-9) in conjunction with a solid tumor between January 2006 and December 2012 (Supplemental Table 1). To assess initial patterns of care and treatment, we limited the

cohort to only those patients with a primary or admitting diagnosis of VTE. VTE diagnoses were grouped into four categories: 1) pulmonary embolism (PE), 2) deep venous thromboembolism (DVT), 3) both deep venous thromboembolism and pulmonary embolism (DVT and PE), and 4) VTE not otherwise specified (NOS). Solid tumors were grouped into the following primary site categories: breast, lung, gastrointestinal, gynecologic, genitourinary, lymphoma, and other (brain, skin, soft-tissue, head and neck).

Clinical and Demographic Characteristics

Demographic and clinical characteristics analyzed included age (<50 years, 50–59, 60–69, 70–79), gender (female or male), race (white, black, Hispanic, or other), marital status (married, single, or other/unknown), and insurance status (Medicare, Medicaid, Private Insurance, other), year of admission (2006–2012), and comorbidity score (Elixhauser index [0, 1, and 2]).²⁰ Hospital characteristics analyzed included region (Northeast, Midwest, South, West), location (urban or rural) size (small, medium, large), teaching status (teaching or non-teaching), and hospital volume. Hospital volume was estimated as the number of VTE patients seen at a given hospital for each year the hospital contributed at least one patient. The distribution of annual hospital volume was used to create quartiles (low, medium-low, medium-high, high). The specialty of the admitting physician was noted for each patient and classified as oncologist, internist (non-hematology/non-oncology), hospitalist, and other.

Main Outcome Measures

The primary goal of the analysis was to evaluate the utilization and predictors of invasive procedures for the management of VTE. We focused on three interventions: insertion of an IVC filter, thrombolytic treatment, and thrombectomy. We defined IVC filter insertion, receipt of thrombolytic therapy, or thrombectomy as present if the procedure was billed at any point during the patient's index hospital admission.

Statistical Analysis

Frequency distributions between categorical variables were compared using χ^2 tests and univariate logistic regression models. We developed hierarchical mixed effects regression models to assess the association between the demographic, clinical, and hospital characteristics of interest and utilization of the interventions. The models included all demographic, clinical, and hospital characteristics, since all predictors were deemed clinically relevant, as well as a hospital-specific intercept to account for hospital level clustering. Statistical tests for significance were analyzed at an alpha level of 5%. All analyses were two sided and conducted with SAS version 9.4 (SAS Institute, Cary, NC).

Results

We identified 32,545 individuals with a primary or admitting diagnosis of VTE in conjunction with an active cancer diagnosis. The median length of stay was 5 days (IQR, 3–7 days), and the in-house mortality rate was 5.3%.

Within the cohort, the median patient age was 68 years (IQR 58–77) (Table 1). The majority of patients were white (69.8%), married (49.8%), and covered by Medicare (59.6%). The most common type of VTE was PE alone (40.3%), and the most common tumor sites for the cohort were lung (30.0%) and gastrointestinal (25.9%) cancer. Nearly two-thirds of the cohort had at least two comorbidities (64.3%). Most patients were seen at hospitals located in the south (43.9%) and in urban areas (87.6%), at non-teaching hospitals (59.8%), and hospitals with less than 400 beds (52.4%).

A total 115 patients (0.4%) underwent thrombectomy. Due to the low frequency of thrombectomy, this intervention was not analyzed further. IVC filters were placed in 23.1% (n=7531) of patients (Table 2). Patients who were between the ages of 80 and 89, Hispanic, and uninsured had the highest proportions of IVC filter placement (24.5%, 29.8%, and 24.7%, respectively). The proportion of patients receiving an IVC filter decreased over time, from 23.4% in 2006 to 21.2% in 2012 ($p=0.01$). Those most likely to receive an IVC filter had both DVT and PE (OR=1.55; 95% CI, 1.45, 1.65), compared to DVT alone. When compared to patients with breast cancer, IVC filter was more likely to be utilized in patients with all other solid tumors. Likewise, patients with more comorbidities (≥ 2) were 46% more likely to receive an IVC filter (OR=1.46; 95% CI, 1.33, 1.60) when compared to patients with no comorbidities. Patients whose attending physician was an oncologist were less likely to receive an IVC filter than patients cared for by other internists (OR=0.85; 95% CI, 0.77, 0.92). Patients at hospitals located in the West (OR=0.81; 95% CI, 0.66, 0.98) and in rural areas (OR=0.70; 95% CI, 0.60, 0.83) were less likely to receive the IVC filter than patients in the Midwest and at urban hospitals.

Thrombolytic therapy was administered to 1.9% (n=600) of the cohort. Patients who were less than 50 years of age, white, and had private insurance were more likely to receive thrombolytic therapy (3.2%, 2%, 2.6%, respectively). Only patients diagnosed in 2012 (OR 1.56, 95% CI 1.13, 2.16) were significantly more likely to receive thrombolytic therapy than when compared to those in 2006. No one tumor site was significantly associated with an increased likelihood of thrombolytic therapy, but patients with multiple comorbidities (≥ 2) were more likely to receive the therapy than patients with no comorbidities (OR=1.45; 95% CI, 1.11, 1.88).

When compared to patients less than 50 years of age, the likelihood of thrombolytic therapy was significantly less for each age category above 50 years; those who were more than 80 years of age were almost 75% less likely to receive thrombolysis when compared to patients younger than 50 (OR=0.26; 95% CI, 0.18, 0.39). Patients who received care at hospitals in the South (OR=0.61; 95% CI, 0.44, 0.84) were also less likely to have received thrombolytic therapy than patients at hospitals in the Midwest. Characteristics related to hospital location, teaching status, size, and annual volume had no significant association with the likelihood of thrombolytic therapy.

Discussion

We identified substantial variation in the use of interventional treatments for cancer patients with VTE. Although the rate of IVC filter placement is decreasing, more than a quarter of

cancer patients with newly diagnosed VTE had filters placed. In contrast, use of thrombolysis and thrombectomy are uncommon.

Previous studies have reported substantial variations in the frequency of IVC filter placement based on hospital and clinical characteristics.^{25,26} A recent administrative claims study found that hospital characteristics, such as bed size and geographic location were significantly associated with IVC filter placement.²⁶ In the present study, however, we noted that after adjustment for a number of important demographic and clinical risk factors, there were no differences in the odds of IVC filter placement for those admitted to teaching hospitals versus non-teaching hospitals. Additionally, hospital size did not appear to be associated with increased IVC filter placement. We did find variation in the odds of IVC filter placement based on two location predictors. Patients at a rural hospital and at hospitals in the western region of the United States were significantly less likely to receive an IVC filter. Further, patients admitted to high-volume hospitals were no more likely to receive an IVC filter than those admitted to a low-volume hospital.

Demographic factors were not significant predictors of IVC filter placement when included in a model adjusted for clinical and hospital factors. Clinical factors, like increased comorbidities and type of tumor, were the most important predictors of IVC filter placement. Patients with brain, head and neck, skin, and soft tissue, were the most likely to receive an IVC filter, perhaps because of the risk of bleeding. This is in accord with prior studies that report increased frequency of IVC filter placement in patients with brain cancer.^{25,27}

Limited information exists on the use of thrombolysis in cancer patients. The ACCP recommends that thrombolytic therapy only be considered in patients with a low risk of bleeding, which suggests that cancer patients are among those less likely to receive the therapy because of a higher risk of bleeding.¹⁷ Further, limited information on its efficacy and utilization in cancer patients suggests that physicians may evaluate patients for the appropriateness of thrombolytic therapy on a case-by-case basis.

For both IVC filter placement and thrombolysis we identified variation in the admitting physician specialty and the odds of treatment. Oncologists had lower odds of recommending IVC filter placement in cancer patients, while physicians with specialties other than internal medicine, oncology, and hospitalists had higher odds of recommending thrombolytic therapy. These findings may represent differences in severity of the underlying thromboembolism and its complications, differences in practice patterns or other patient-specific factors. Prior studies have also identified differences in practice patterns between oncologists and non-oncologists in the management of cancer-associated complications.¹⁹

We recognize a number of important limitations. The Perspective database contains in-hospital admission information, and thus lacks data on longitudinal follow up. We also lack information to describe the timing of the interventions during hospitalization. We lack data on tumor characteristics and disease course as well as other potential unmeasured confounders that may have influenced treatment. Particularly for those patients with metastatic disease, concern for ongoing risk of progression of VTE may have influenced

treatment choices. Lastly, as with any study of administrative data, information on individual patient and physician preferences were lacking.

IVC filter use and thrombolytic therapy are of particular interest from a public health perspective because of the increased complications in cancer patients who are diagnosed with VTE. Contraindications for traditional anticoagulants lead to variable utilization of more invasive treatments. In addition to more defined indications for use of these invasive treatments in cancer patients, further research to better elucidate why patients received these invasive treatments, particularly IVC filters, when they remain unproven is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Receipt of IVC Filter and Thrombolysis by type of VTE

Table 1

Clinical and demographic characteristics of the cohort.

Characteristic	n	%
	32,545	
<i>Demographic</i>		
Age at diagnosis, year		
<50	3049	9.4
50–59	5872	18.0
60–69	9003	27.7
70–79	8848	27.2
80–89	5773	17.7
Gender		
Female	16542	50.8
Male	16003	49.2
Race		
White	22716	69.8
Black	4338	13.3
Hispanic	893	2.7
Other	4598	14.1
Marital status		
Married	16206	49.8
Single	12725	39.1
Other or unknown	3614	11.1
Insurance		
Medicare	19058	58.6
Medicaid	2486	7.6
Commercial	9382	28.8
Self-pay	596	1.8
Other	1023	3.1
<i>Clinical</i>		
VTE type		
DVT	9564	29.4
PE	13103	40.3
DVT and PE	9440	29.0
Other	438	1.3
Year of diagnosis		
2006	4161	12.8
2007	4150	12.8
2008	4040	12.4
2009	4464	13.7
2010	5010	15.4
2011	5463	16.8

Characteristic	n	%
2012	5257	16.2
Tumor site		
Breast	3066	9.4
Lung	9761	30.0
Gastrointestinal	8422	25.9
Gynecologic	2772	8.5
Genitourinary	5092	15.6
Lymphoma	624	1.9
Other	2808	8.6
Comorbidity score, Elixhauser Index		
0	4042	12.4
1	7563	23.2
2	20940	64.3
<i>Hospital</i>		
Attending Physician Specialty		
Internal Medicine	12456	38.3
Hospitalist	5386	16.5
Oncologist	6369	19.6
Other	8334	25.6
Region		
Midwest	6647	20.4
Northeast	6927	21.3
South	14298	43.9
West	4673	14.4
Location		
Urban	28519	87.6
Rural	4026	12.4
Teaching status		
Teaching	13097	40.2
Non-teaching	19448	59.8
Hospital Size, beds		
< 400	17039	52.4
400–600	8911	27.4
> 600	6595	20.3
Hospital Volume		
Quartile 1	8132	25.0
Quartile 2	8094	24.9
Quartile 3	8243	25.3
Quartile 4	7977	24.5

Clinical and demographic characteristics associated with placement of inferior vena cava (IVC) filter and thrombolysis

Table 2

Characteristic	IVC Filter			Odds Ratios			Thrombolysis			Odds Ratios		
	N (%) ^a	p-value	Univariable	Multivariable (95% CI)	Referent	N (%) ^a	p-value	Univariable	Multivariable (95% CI)	Referent	N (%) ^a	p-value
Total No.	7531 (23.1)					600 (1.8)						
<i>Demographic</i>												
Age at diagnosis, year		0.004					<.0001					
<50	682 (22.4)		Referent		Referent	97 (3.2)		Referent		Referent		
50–59	1275 (21.7)		0.96	0.89 (0.79, 0.99)		147 (2.5)		0.78	0.70 (0.54, 0.92)			
60–69	2069 (23)		1.04	0.91 (0.82, 1.02)		172 (1.9)		0.59	0.50 (0.38, 0.67)			
70–79	2089 (23.6)		1.07	0.93 (0.82, 1.05)		118 (1.3)		0.41	0.34 (0.24, 0.48)			
80–89	1416 (24.5)		1.13	0.95 (0.83, 1.08)		66 (1.1)		0.35	0.26 (0.18, 0.39)			
<i>Gender</i>												
Female	3737 (22.6)	0.02	Referent		Referent	315 (1.9)	0.41	Referent		Referent		
Male	3794 (23.7)		1.07	1.01 (0.95, 1.08)		285 (1.8)		0.93	0.91 (0.74, 1.11)			
<i>Race</i>												
White	5166 (22.7)	<.0001	Referent		Referent	458 (2)	0.01	Referent		Referent		
Black	1008 (23.2)		1.03	1.03 (0.94, 1.12)		61 (1.4)		0.69	0.69 (0.52, 0.93)			
Hispanic	266 (29.8)		1.44	0.95 (0.79, 1.15)		13 (1.5)		0.72	0.82 (0.45, 1.49)			
Other	1091 (23.7)		1.06	1.07 (0.96, 1.19)		68 (1.5)		0.7	0.81 (0.59, 1.10)			
<i>Marital status</i>												
Married	3719 (22.9)	0.01	Referent		Referent	316 (1.9)	0.01	Referent		Referent		
Single	2901 (22.8)		0.99	0.99 (0.93, 1.05)		241 (1.9)		0.97	1.06 (0.88, 1.27)			
Other or unknown	911 (25.2)		1.13	1.06 (0.93, 1.2)		43 (1.2)		0.61	0.71 (0.48, 1.06)			
<i>Insurance</i>												
Medicare	4480 (23.5)	0.005	Referent		Referent	281 (1.5)	<.0001	Referent		Referent		
Medicaid	513 (20.6)		0.85	0.92 (0.81, 1.05)		52 (2.1)		1.43	0.83 (0.58, 1.2)			
Commercial	2181 (23.2)		0.99	1.05 (0.96, 1.14)		240 (2.6)		1.75	1.14 (0.90, 1.45)			
Self-pay	147 (24.7)		1.07	1.17 (0.94, 1.44)		11 (1.8)		1.26	0.84 (0.44, 1.6)			
Other	210 (20.5)		0.84	0.92 (0.78, 1.1)		16 (1.6)		1.06	0.70 (0.41, 1.21)			
<i>Clinical</i>												

Characteristic	IVC Filter		Odds Ratios		Thrombolysis		Odds Ratios	
	N (%) [*]	p-value	Univariate	Multivariable (95% CI)	N (%) [*]	p-value	Univariate	Multivariable (95% CI)
VTE type		<.0001				<.0001		
DVT	2503 (26.2)		Referent	Referent	244 (2.6)		Referent	Referent
PE	1689 (12.9)		0.42	0.43 (0.4, 0.46)	131 (1)		0.39	0.34 (0.27, 0.42)
DVT and PE	3331 (35.3)		1.54	1.55 (1.45, 1.65)	209 (2.2)		0.87	0.79 (0.65, 0.96)
VTE NOS	8 (1.8)		0.05	0.05 (0.02, 0.10)	16 (3.7)		1.45	1.37 (0.80, 2.34)
Year of diagnosis		0.01				0.08		
2006	972 (23.4)		Referent	Referent	65 (1.6)		Referent	Referent
2007	1005 (24.2)		1.05	1.02 (0.92, 1.13)	73 (1.8)		1.13	1.11 (0.79, 1.56)
2008	958 (23.7)		1.02	0.98 (0.88, 1.09)	61 (1.5)		0.97	0.98 (0.68, 1.41)
2009	1064 (23.8)		1.03	0.94 (0.84, 1.04)	86 (1.9)		1.24	1.25 (0.89, 1.75)
2010	1157 (23.1)		0.99	0.90 (0.81, 1.00)	85 (1.7)		1.09	1.10 (0.79, 1.55)
2011	1263 (23.1)		0.99	0.89 (0.80, 0.99)	112 (2.1)		1.32	1.36 (0.98, 1.87)
2012	1112 (21.2)		0.88	0.78 (0.70, 0.87)	118 (2.2)		1.45	1.56 (1.13, 2.16)
Tumor site		<.0001				0.002		
Breast	448 (14.6)		Referent	Referent	54 (1.8)		Referent	Referent
Lung	2183 (22.4)		1.68	1.68 (1.49, 1.89)	142 (1.5)		0.82	0.93 (0.67, 1.31)
Gastrointestinal	2138 (25.4)		1.99	1.79 (1.58, 2.02)	171 (2)		1.16	1.18 (0.84, 1.64)
Gynecologic	735 (26.5)		2.11	1.89 (1.65, 2.17)	69 (2.5)		1.42	1.18 (0.82, 1.71)
Genitourinary	1107 (21.7)		1.62	1.45 (1.26, 1.66)	105 (2.1)		1.17	1.41 (0.97, 2.07)
Lymphoma	81 (13)		0.87	0.82 (0.63, 1.07)	16 (2.6)		1.47	1.23 (0.68, 2.21)
Other	839 (29.9)		2.49	2.29 (1.99, 2.64)	43 (1.5)		0.87	0.71 (0.47, 1.10)
Comorbidity score, Elixhauser Index		<.0001				0.01		
0	744 (18.4)		Referent	Referent	75 (1.9)		Referent	Referent
1	1569 (20.7)		1.16	1.14 (1.03, 1.26)	108 (1.4)		0.77	0.90 (0.66, 1.22)
2	5218 (24.9)		1.47	1.46 (1.33, 1.60)	417 (2)		1.08	1.45 (1.11, 1.88)
<i>Hospital</i>								
Attending Physician Specialty		<.0001				0.01		
Internal Medicine	3032 (24.3)		Referent	Referent	192 (1.5)		Referent	Referent
Hospitalist	1167 (21.7)		0.86	1.02 (0.93, 1.13)	105 (1.9)		1.27	1.15 (0.87, 1.50)
Oncologist	1238 (19.4)		0.75	0.85 (0.77, 0.92)	121 (1.9)		1.24	1.11 (0.86, 1.44)

Characteristic	IVC Filter		Odds Ratios		Thrombolysis		Odds Ratios	
	N (%) [*]	p-value	Univariate	Multivariable (95% CI)	N (%) [*]	p-value	Univariate	Multivariable (95% CI)
Other	2094 (25.1)		1.04	1.07 (1.00, 1.15)	182 (2.2)		1.43	1.36 (1.10, 1.69)
Region		<.0001				0.004		
Midwest	1543 (23.2)		Referent	Referent	147 (2.2)		Referent	Referent
Northeast	1882 (27.2)		1.23	1.28 (1.06, 1.55)	134 (1.9)		0.87	0.86 (0.58, 1.25)
South	3215 (22.5)		0.96	1.00 (0.86, 1.17)	222 (1.6)		0.7	0.61 (0.44, 0.84)
West	891 (19.1)		0.78	0.81 (0.66, 0.98)	97 (2.1)		0.94	0.93 (0.63, 1.37)
Location		<.0001				0.88		
Urban	6811 (23.9)		Referent	Referent	527 (1.8)		Referent	Referent
Rural	720 (17.9)		0.69	0.70 (0.6, 0.83)	73 (1.8)		0.98	1.15 (0.81, 1.63)
Teaching status		<.0001				0.26		
Teaching	3245 (24.8)		Referent	Referent	255 (1.9)		Referent	Referent
Non-teaching	4286 (22)		0.86	0.92 (0.79, 1.06)	345 (1.8)		0.91	1.04 (0.77, 1.39)
Hospital Size, beds		0.0001				0.03		
< 400 (low)	3781 (22.2)		Referent	Referent	283 (1.7)		Referent	Referent
400–600 (medium)	2177 (24.4)		1.13	1.12 (0.96, 1.32)	185 (2.1)		1.26	1.14 (0.83, 1.58)
> 600 (high)	1573 (23.9)		1.1	1.10 (0.86, 1.42)	132 (2)		1.21	1.38 (0.87, 2.20)
Hospital Volume, annualized		<.0001				0.06		
Quartile 1	1713 (21.1)		Referent	Referent	124 (1.5)		Referent	Referent
Quartile 2	1876 (23.2)		1.13	1.18 (1.01, 1.37)	146 (1.8)		1.19	1.26 (0.91, 1.75)
Quartile 3	2098 (25.5)		1.26	1.21 (1.01, 1.44)	170 (2.1)		1.34	1.33 (0.93, 1.91)
Quartile 4	1844 (23.1)		1.13	0.97 (0.75, 1.25)	160 (2.0)		1.32	1.25 (0.78, 2.02)

*
presented as row percent