Title

Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE): patterns of use and outcomes

Authors

Brunson, Ann
Ho, Gwendolyn
White, Richard
et al.

Publication Date

2016-04-01

DOI

10.1016/s0049-3848(16)30112-8

Peer reviewed

Thrombosis Research 140S1 (2016) S132–S141

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE): patterns of use and outcomes

Ann Brunson[a], Gwendolyn Ho[a], Richard White[b], Ted Wun[a,b,c,d*]

[a] Center for Oncology Hematology Outcomes Research and Training (COHORT), Division of Hematology Oncology, UC Davis School of Medicine
[b] Division of General Internal Medicine, UC Davis School of Medicine
[c] UC Davis Clinical and Translational Sciences Center
[d] Division of Hematology Oncology, VA Northern California Healthcare System

KEYWORDS

Cancer and thrombosis
Inferior vena cava filter
Venous thromboembolism
Deep venous thrombosis
Pulmonary embolism
Outcomes

ABSTRACT

Background: Few studies have evaluated the use and outcomes of inferior vena cava filters (IVCF) insertion in cancer patients with deep venous thrombosis (DVT) or pulmonary embolism (PE).
Methods: Hospital records of patients with a principal diagnosis of lower extremity DVT and/or PE and cancer in California between January 1, 2005 and December 31, 2009 were analyzed. Multivariable logistic regression analysis was used to identify variables associated with IVCF use and propensity matched methodology was used to determine the effect of IVCF insertion on clinical outcomes.
Results: An IVCF was placed in 19.6% of 14,000 cancer patients and VTE. This varied widely across hospitals, from 0% to 52%, and by cancer type. The strongest predictors of IVCF use were a diagnosis of brain cancer (OR=4.6, CI: 3.7-5.6), undergoing major surgery (OR=4.9, CI: 3.9-6.1), and bleeding (OR=2.7, CI: 2.0-3.5). Only 21% of patients with IVCF had a strong contraindication to anticoagulation (bleeding or major surgery). There was no benefit for 30-day mortality and no reduction in subsequent PE (+/- DVT). Additionally, there was 60% increased risk of recurrent DVT and 20% increased risk of subsequent bleeding when an IVCF was placed.
Conclusions: An IVCF was placed in approximately 20% of acute VTE patients with cancer and use varied widely between hospitals and cancer types. Most patients did not have a contraindication for anticoagulation. There was no benefit in short-term mortality or risk of PE; there was increased risk of DVT and subsequent bleeding.

Inferior vena cava filters (IVCFs) are frequently inserted in patients who are hospitalized for acute venous thromboembolism (VTE). If anticoagulant treatment cannot be given, placement of an IVCF may be the only treatment option available to reduce the risk of pulmonary embolism (PE). However, there is no strong evidence that use of a IVCF prevents either death or further pulmonary embolism (PE) [1-3]. Rather, observational studies of VTE patients treated with a IVCF in conjunction with anticoagulant therapy have reported numerous thrombotic and embolic complications [4-9].

In a study of IVCF use in California hospitals [10], White et al. observed wide variation in the use of IVCFs, from 0% to 39%, among patients admitted to a wide spectrum of hospitals with a principal diagnosis of VTE, even after adjusting for important clinical covariates. These findings suggest that patients with similar clinical characteristics are being treated or not treated with an IVCF based largely on local prevalent practice pattern. The frequency of IVCF use in the management of patients with acute VTE has expanded exponentially, with one study showing a 20-fold increase between 1979-1999 [11].

In two relatively small, randomized clinical trials, IVCF use was studied in patients with acute DVT [3] and acute PE [12] who also received standard anticoagulation therapy. Retrievable inferior vena cava filter use provided no significant survival benefit and did not reduce the frequency of subsequent PE in patients who presented with PE [12]. In the study of patients who presented with acute DVT (randomized to a permanent or no IVCF), the incidence of pulmonary embolism was decreased in patients randomized to IVCF use, but recurrent VTE manifested as acute DVT was increased and the investigators did not recommend their routine use [3].

The American College of Chest Physicians 2012 guidelines recommend against the use of IVCF in patients with acute VTE except in patients who have a contraindication to therapeutic anticoagulation, such as patients with active bleeding or patients who require surgery [13].

IVCF use in patients with cancer

Acute venous thromboembolism (VTE) is a common cause of morbidity and mortality in cancer patients [14]. Cancer patients

* Corresponding author at: Division of Hematology Oncology, UC Davis Comprehensive Cancer Center, 4501 X Street, Sacramento, CA 95817, USA. Tel.: +1-916-734-3772; fax: +1-916-734-7946.
E-mail address: twun@ucdavis.edu (T. Wun).

0049-3848/

have a higher risk of developing incident VTE compared to matched non-cancer patients [15,16], they have a higher risk of recurrent VTE [17,18], and development of VTE in cancer patients is associated with higher mortality [19-21]. The management of acute VTE in cancer patients is challenging because they have an increased risk of developing major bleeding during anticoagulation therapy [17]. The use of IVCFs has emerged as a particularly common therapeutic modality in patients with cancer in the United States although the clinical benefit in this setting is also controversial [22,23]. In the study by White et al. cited above, cancer patients had 70% higher odds of IVCF use compared to patients without cancer [10].

Although IVCF placement in cancer patients appeared to be common, there had been no studies that determined the factors associated with more frequent use of IVCFs in patients with cancer. Therefore our group determined the clinical, demographic and hospital characteristics associated with IVCF use in cancer patients, which has been reported earlier and reviewed herein [24]. There is also little data on whether IVCF placement affects outcomes in patients with cancer-associated acute VTE. Therefore, we also sought to determine the effect of IVCF in cancer patients with acute VTE admitted to hospital on four important clinical outcomes: early death, recurrent deep venous thrombosis, recurrent pulmonary embolism, and major bleeding. We conducted a retrospective cohort study using a large retrospective administrative dataset.

Methods

This was a retrospective cohort to analyze factors associated with IVCF placement and outcomes of adults with acute VTE and an active cancer diagnosis hospitalized in California between January 1, 2005 and December 31, 2009. Patients either received an IVC filter or did not during the index hospitalization as treatment for the acute VTE. Only the first admission for acute VTE for a unique patient was used. Specific outcomes included 30-day mortality, recurrent VTE (manifested as PE or DVT), and subsequent major bleeding. The California Health and Welfare Agency Committee for the Protection of Human Subjects, and the University of California, Davis Institutional Review Board approved this study.

Databases

The California Patient Discharge Database (PDD) contains information about all patients hospitalized in the state, except patients admitted to one of 14 Federal hospitals (12 Veterans Affairs hospitals and two military hospitals). The Emergency Department Utilization (EDU) dataset contains information on all emergency department visits, again with exception of the Federal facilities. Serial records from a single person can be linked using an encrypted form of the social-security number, called the record linkage number (RLN) [25,26]. All PDD records include demographic information, insurance status (e.g. self-pay, Medicare, insurance, etc.), a principal medical diagnosis, up to 24 additional 'secondary' diagnoses, and a principal and up to 20 secondary procedures coded using International Classification of Diseases, 9th Revision, Clinical Modification codes (ICD-9-CM). Since 1996 all medical diagnoses in the PDD required a present-on-admission (POA) indicator. The database also includes a hospital identifier with the ability to link to hospital characteristics (e.g. public, academic, for-profit, etc.) and location (rural vs. urban).

Acute VTE

All cases admitted with a principal diagnosis of either acute DVT in the lower extremity or acute PE between Jan 1, 2005 and Dec 31, 2009 were first identified. Cases diagnosed with hospital-acquired acute VTE only were identified by the presence of a secondary diagnosis code for acute VTE coupled with a POA indicator of no (POA=N). Hospital-acquired VTE cases were excluded to ensure that VTE occurred prior to filter placement. For each linked record, we selected only the first hospitalization for acute-VTE during the study period.

Cancer cases

Cases were categorized as having cancer based on the presence of a cancer diagnosis code at the time of admission or within a 6 month time period prior to the index hospitalization. Cases with unknown cancer primary site were excluded from the cohort. Cancer type was categorized by "perceived" bleeding risk (high bleed risk-brain, high bleed risk-acute leukemia, moderate bleed risk-urinary and kidney, and low bleed risk-all others). The within-hospital frequency of IVCF placement in cases with and without cancer was also compared.

Vena cava filter use

All cases hospitalized for acute VTE with cancer that had a IVCF placed were identified by procedure code 38.7 (interruption of the vena cava). Although this procedure code is also used for vena cava plication, ligation or other interruption, these other procedures are rarely performed [27,28]. All of the cases with acute VTE that had an IVCF placed any time prior to Jan 1, 2005 were excluded. The frequency of VCF use was calculated as the number of hospitalizations that included VCF placement divided by the corresponding total number of hospitalizations for acute VTE.

Hospitals

Optimally the frequency of IVCF use should be compared only among hospitals that admitted at least a minimal number of VTE cases. We targeted hospitals that admitted a minimum of 55 or more acute VTE hospitalizations over the 6-year study period in our previous analysis of non-cancer cases [10], the current study required the same but there was no minimal number of cancer cases. This cut-off of 55 hospitalizations was chosen in order ensure that there were a sufficient number of chances for IVCF insertion to guarantee that the 95% confidence limits on the calculated frequency of IVCF use was not wider than 10%, assuming that the average frequency of VCF use was 15%. The within hospital IVCF use correlation between cancer and non-cancer patients was restricted to hospitals with at least 55 acute VTE cases, and 15 or more acute VTE cancer patients (223 hospitals) in order to improve the reliability of this calculation.

Active bleeding

Cases with bleeding were identified using ATRIA Study identified set of ICD-9-CM codes [29,30]. Cases were classified as having intracranial bleeding, gastrointestinal bleeding, or "other" bleeding. Hematuria alone and epistaxis were included only if the patient also received a blood transfusion. Bleeding was categorized as either present at the time of admission or that developed during the hospital stay using the POA flag (Y/W = on admission, N/U = during the hospitalization). Having active bleeding was considered a contraindication to anticoagulation.

Surgery

Major operating room procedures were identified using a set of ICD-9-CM codes used by the Centers for Medicare and Medicaid Services. This list was modified to exclude relatively minor operating room procedures such as cosmetic surgery, and endoscopic procedures commonly performed outside of the operating room, such as upper gastrointestinal endoscopy, colonoscopy and cystoscopy. Vascular procedures commonly performed in conjunction with

either thrombolysis, venous stenting or placements of a IVCF were analyzed separately.

Major surgery was defined as undergoing a major operation during the index hospitalization. Prior surgery was defined as undergoing surgery within 7 days prior to the index hospitalization. Undergoing surgery was also considered a contraindication to anticoagulation.

Co-morbidity and severity-of-illness

Chronic co-morbid conditions (up to 26) were defined using the Elixhauser co-morbidity software [31,32]. Cancer was not counted as a co-morbidity in this analysis. Cases with cancer were classified as having metastatic cancer (ICD-9-CM 196.0-199.9) or non-metastatic cancer (ICD-9-CM 140.0-195.9, 200.0-209.9). Proprietary software from 3M™ (APR-DRG grouper, V-24) was applied to every record to determine the severity-of-illness (SOI) at the time of admission, which was classified as mild, moderate, major or extreme [33]. Risk-of-mortality score (1-4) is also calculated with this software.

Outcomes

The principal outcome was death less than or equal to 30 days from index admission, recurrent VTE (manifested as PE or DVT) less than or equal to 180 days from discharge of the index admission, and subsequent bleed less than or equal to 180 days from discharge of index admission. Recurrent VTE was defined as an acute VTE re-admission to either a PDD or EDU hospital, or as a hospital acquired VTE (POA code= No/Unknown) during a subsequent PDD hospitalization. Subsequent bleeding was identified using specific ICD-9-CM codes that were classified as intracranial, gastrointestinal, and other. Bleeds in the other category had to be accompanied by a transfusion procedure code (ICD-9-CM = 99.00, 99.03, 99.04-99.07).

Statistical methods

Propensity score

Propensity score methodology was used to balance the IVC filter and NO IVC filter groups. A propensity score for IVC filter placement was created using a logistic regression model that included demographic and hospital characteristics as well as specific clinical covariates such as active bleeding, surgery, perceived bleeding risk cancer group, and metastatic disease. The outcome models used inverse probability weight (IPW) [34]. The standardized mean differences in baseline covariates between the IVC filter group and NO IVC filter groups were used to determine the effectiveness of the propensity score adjustment.

Immortal time bias

IVC filter placement was accompanied by a procedure date. Because filter placement varied from early to late during the index admission, analysis of the effect of IVC filter placement on early mortality is subject to immortal time bias [35-37]. Patients in the filter group had to be alive at time of insertion, whereas some in the NO filter group might have died before having the opportunity for IVC filter placement. To correct for this bias, IVC filter insertion was used as a time dependent covariate in the mortality model.

Outcomes

Outcome models used cox proportional hazard methodology after testing the proportional hazard assumption. Mortality modeled time from index admission date to death or 30 days. For recurrent VTE and bleeding, death was considered non-informative censoring. Categorical data was analyzed using chi-square testing and two-sided p-values less than 0.05 were considered statistically significant. Analyses were performed using SAS® Version 9.4.

Results

Characteristics of cancer patients that received an IVC filter for acute VTE

A total of 87,150 cases were identified with a principal diagnosis code of VTE, either pulmonary embolism or lower extremity deep venous thromboembolism. We excluded cases with no active cancer (N=71,996) or cancer with unknown primary site (N=1090). We also excluded cases from hospitals with less than 55 acute VTE cases (N=64). Our final cohort included a total of 14,000 patients admitted with acute VTE and cancer, but without any prior record of having a IVCF placed (Figure 1). Bleeding occurred in 5.6% of all cases and a major surgery was noted in 2.6%. An IVCF was inserted in 19.6% of the cancer cases. The frequency of IVCF use varied widely between hospitals with a range of 0% to 52% among 223 hospitals that had more than 55 acute VTE hospitalizations and 15 or more of these in patients with cancer.

There were 7,194 filters placed amongst 64,348 acute VTE cases that did not have cancer (11.2%). Figure 2 shows the correlation between the frequency of filter use in the cancer and non-cancer cases. For most hospitals, the use of IVCFs was greater in cancer patients with acute VTE compared to non-cancer patients. There was a high correlation in the frequency of VCF use in non-cancer and cancer patients within a hospital ($r=0.71$, $R^2=0.51$).

The frequency distribution of IVCF use, and proportions of patients with IVCF placement that had bleeding and surgery, by cancer type is shown in Figure 3**.** Cases with brain cancer had the highest frequency of VCF use (43%) whereas it was much lower in patients with lymphoma (13%), leukemia (13%), breast (12%) and lip/oral cancer (8%). Of note, in the cases with brain cancer and VTE that had an IVCF placed, only 9% had bleeding and 9% surgery (some had both). As shown in Figure 3, the proportion of patients within each tumor type with contraindication to anticoagulation (bleeding or surgery) also greatly varied.

The bivariate frequency of IVCF use based on clinical/demographic, socioeconomic, and hospital-characteristics is shown in Table 1. There was no significant difference in IVCF use based on race/ethnicity, insurance status or type of facility. Among these cases with acute VTE, the frequency of IVCF placement was higher in the cases with active bleeding (47.0%), brain cancer (43.0%), major surgery (58.4%), cases with metastatic cancer (22.0%) and cases with a greater number of comorbid conditions or increasing severity of illness at the time of admission. The use of IVCFs was low in hospitals with fewer than 100 beds (7.5%) but similar in hospitals with 100-200 beds (17.4%) and those with over 200 beds (20.8%). Use of IVCFs was only 14.1% in Kaiser hospitals (a large vertically integrated health maintenance organization that cares for a significant proportion of the population in California) compared to 19% in teaching hospitals and 21.1% in private hospitals. Use in rural hospitals was quite low, 6.5% compared to urban hospitals (20.2%).

The multivariable logistic regression model analyzing predictors of IVCF use is shown in Table 2. The strongest predictors of IVCF use were having brain cancer (OR=4.6, 95% CI: 3.7-5.6), major surgery during the hospitalization (OR = 4.9, 95% CI: 3.9-6.1), bleeding at the time of admission (OR=2.7, 95% CI: 2.1-3.5), bleeding during the hospitalization (OR=2.7, 95% CI: 1.9-3.9); major severity-of-illness (OR=1.9, 95% CI: 1.5-2.4), extreme severity-of-illness (OR=1.8, 95% CI: 1.4-2.4) and metastatic cancer (OR=1.5, 95% CI: 1.3-1.6).

Differences by hospital characteristics found on univariate analysis were confirmed in the adjusted multivariable model. Smaller and rural hospitals were less likely to place IVCF in patients with cancer and acute VTE: fewer than 100 licensed beds (OR= 0.4; 95% CI 0.3-0.5; 100-199 licensed beds (OR= 0.9, 95% CI: 0.8-1.0); and rural location versus urban (OR= 0.4; 95% CI: 0.3-0.5). Private hospitals had significantly greater odds of using an IVCF

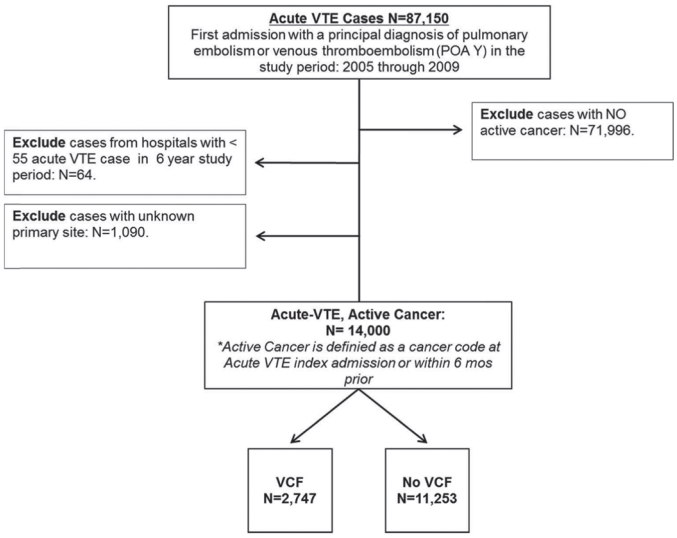

Fig. 1. Cohort diagram. Reprinted with permission [24].

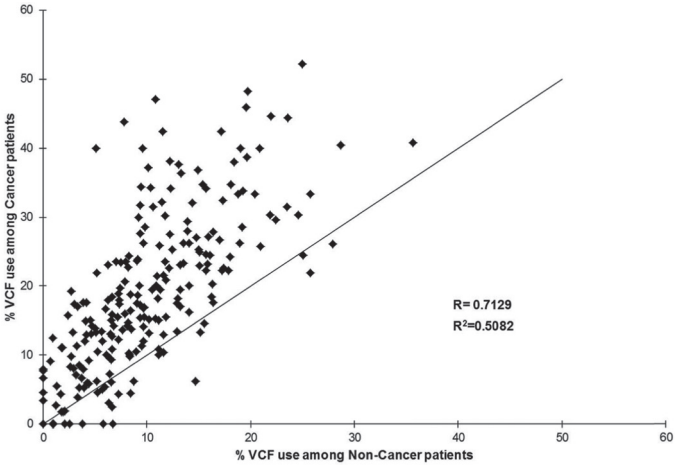

Fig. 2. Correlation of VCF placement for acute VTE in cancer versus non-cancer patients in California hospitals. Excludes hospitals with <15 cancer/acute VTE cases. Reprinted with permission [24].

compared to non-teaching Kaiser Foundation hospitals. There was no significant difference in the odds of IVCF use when profit and not-for-profit hospitals were compared. This logistic model had a c-statistic of 0.702.

Effect of IVCF on outcomes in patients with cancer and thrombosis

Using an adjusted propensity score model, standardized mean differences are shown in Figure 4. These figures illustrate that IPW reduces the differences at the baseline characteristics for the IVCF treatment group vs. the no IVCF treatment group.

Short-term mortality (death ≤ 30 days) from the index admission date showed no benefit for IVCF treatment (HR: 1.12, CI: 0.99-1.26). Metastatic disease (HR: 1.79, CI: 1.52-2.10) and risk of mortality were strong predictors of short-term mortality. There was no reduction in the risk of a recurrent PE (+/- DVT) at 180 days or less from index admission discharge (HR: 0.81, CI: 0.60-1.08). Patients with a diagnosis of brain cancer were 1.9-fold more likely to have a recurrent PE compared to most solid tumors with a perceived low risk of bleeding. There was a 56% increase in recurrent VTE manifested as DVT at 180 days or less for patients treated with an IVCF compared to those not treated with an IVCF (HR: 1.56, CI: 1.26-1.92). Hispanic race was the only other independent significant

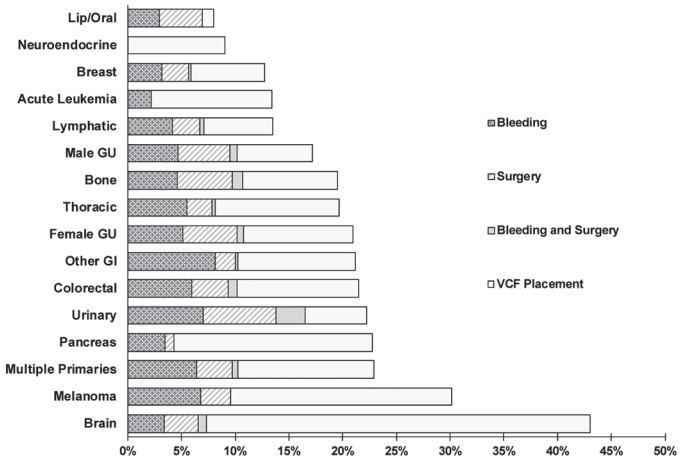

Fig. 3. Frequency of VCF placement, bleeding and surgery by cancer type. Bleeding includes those that had bleeding at the time of admission and/or during the index hospitalization. Surgery includes those that underwent a major operation during hospitalization or 7 days prior. Reprinted with permission [24].

predictor for recurrent DVT. Additionally, IVCF treated patients were 1.2-fold more likely to have a bleeding occur at 180 days or less from index admission discharge (HR: 1.20, CI: 1.04-1.38). These results are shown in Figures 5-8.

Discussion

There is wide variation in frequency of IVCF use in cancer patients among California hospitals with significant variation depending on the underlying type, metastatic status, and perceived bleeding risk of the cancer. The frequency of IVCF use in cancer patients also differed depending on hospital and clinical characteristics. There appears to be no benefit to IVCF filter placement in terms of 30-day mortality and recurrent PE. Consistent with results of randomized studies in non-cancer patients, there was increased hazard of recurrent DVT [3]. IVCF placement was also associated with a higher risk of bleeding.

In a previous study, the frequency of IVCF placement for all patients with acute VTE varied among 263 California hospitals from 0 to 39%. We found an even wider variation in the frequency of IVCF use in the cancer patients with acute VTE, from 0-52%. Even after adjusting for important factors that might influence the decision to use an IVCF, such as bleeding, undergoing surgery, metastases, and the number of chronic comorbidities, hospital characteristics were still significantly predictive of IVCF use. Admission to a larger, urban and private hospital was associated with greater odds of having a vena cava filter placed. There was also a strong correlation between IVCF placement between cancer and non-cancer patients. This finding suggests that local practice pattern within a hospital affects the use of IVCFs. We also speculate that larger private and teaching hospitals may have greater availability of specialists who place IVCFs.

The variation in the frequency of IVCF placement between cancer types was quite striking, with a very high percentage of cases with brain cancer receiving an IVCF, but also frequent use in patients with melanoma and cancer involving the pancreas, female genital tract, colon and urinary tract. However, variable proportions of cases had a clear contraindication for anticoagulation (surgery, active bleeding), despite the high frequency of IVCF placement (Figure 3). In certain malignancies the use of IVCFs occurred primarily in those patients undergoing surgery or having active bleeding. However, in other cancers including melanoma, leukemia and brain, IVCF placement occurred despite the lack of a clear contraindication to anticoagulation.

Table 1
Characteristics of Cancer Patients Hospitalized for Acute VTE

		All	Filter		
Variables		N	N	%	P value
Total		14,000	2,747	19.6%	
Age	Age <50	1,539	259	16.8%	0.0423
	50-59	2,334	456	19.5%	
	60-69	3,500	694	19.8%	
	70-79	3,811	755	19.8%	
	80+	2,816	583	20.7%	
Gender	Male	6,903	1,438	20.8%	0.0004
	Female	7,097	1,309	18.4%	
Cancer Type - Perceived Bleed Risk	High- Brain	530	228	43.0%	<0.0001
	High- Acute Leukemia	89	12	13.5%	
	Mid- Bladder, Kidney	738	164	22.2%	
	Low- everything else	12,643	2,343	18.5%	
Metastatic	Yes	6,100	1,344	22.0%	<0.0001
	No	7,900	1,403	17.8%	
Bleeding	POA Yes	575	265	46.1%	<0.0001
	POA No	215	106	49.3%	
	No Bleeding	13,210	2,376	18.0%	
Bleeding Category	ICH	43	27	62.8%	0.0047
	GI	424	212	50.0%	
	Other/Transfusion	323	132	40.9%	
Thrombolytic RX	Yes	253	82	32.4%	<0.0001
	No	13,747	2,665	19.4%	
Major Surgery	Yes	361	211	58.4%	<0.0001
	No	13,639	2,536	18.6%	
Vascular Surgery	Yes	193	73	37.8%	<0.0001
	No	13,807	2,674	19.4%	
Comorbidities	None	1,919	258	13.4%	<0.0001
	1-2	6,291	1,124	17.9%	
	3+	5,790	1,365	23.6%	
VTE Type	PE (± DVT)	7,999	1,380	17.3%	<0.0001
	Proximal DVT	3,967	886	22.3%	
	Distal DVT	2,034	481	23.6%	
Severity of Illness	SOI-Minor	1,194	119	10.0%	<0.0001
	SOI-Moderate	6,508	1,081	16.6%	
	SOI-Major	5,429	1,316	24.2%	
	SOI-Extreme	869	231	26.6%	
Facility Size	0-99 Beds	589	44	7.5%	<0.0001
	100-199 Beds	2,545	444	17.4%	
	200+ Beds	10,866	2,259	20.8%	
Facility Type	Kaiser	2,275	321	14.1%	<0.0001
	Teaching	2,021	383	19.0%	
	Private	9,704	2,043	21.1%	
Facility Location	Rural	582	38	6.5%	<0.0001
	Urban	13,418	2,709	20.2%	
Kind of Facility	Non-Profit	10,660	2,123	19.9%	0.1174
	For-Profit	3,340	624	18.7%	

PE = Pulmonary Embolism; DVT = Deep Vein Thrombosis; POA = Present on admission
Reprinted with permission [24].

We hypothesized that part of this variation would be due to a perceived higher risk of bleeding in certain cancer types. Indeed in the adjusted model, having brain cancer was associated > 4-fold odds of IVCF placement. However, having other malignancies often perceived to be associated with higher risk of bleeding such as acute leukemia, bladder and kidney cancer were not significant predictors of IVCF placement when adjusted for other covariates. The high rate of IVCF placement in melanoma patients was also unexpected, but may be due to a perception that melanoma has a high bleeding risk as a highly vascular malignancy and/or the presence of brain metastases.

Literature on the use of IVCFs in patients with brain cancer is inconclusive. In this study, we found that almost half of all brain cancer patients had a IVCF placed but only 9% of these patients had active bleeding and 9% had major surgery at the time of the index hospitalization or prior 7 days. The high frequency of IVCF

Table 2
Multi-variable model to predict use of VCF among cancer patients with acute VTE

Variables	OR	(95% CI)	P value
Gender (vs. Male)			
Female	0.9	(0.79, 0.95)	0.0020
Race/Ethnicity (vs. NH White)			
African American	1.0	(0.85, 1.16)	0.9654
Hispanic	0.9	(0.82, 1.09)	0.4208
Asian/PI	1.0	(0.81, 1.22)	0.9279
Other/Unknown	0.9	(0.67, 1.21)	0.4726
Age (continuous, 10 year increase)	1.1	(1.01, 1.11)	0.0107
Insurance Coverage (vs. Medicare)			
Medi-Cal	0.9	(0.77, 1.11)	0.4071
Private	1.2	(1.03, 1.33)	0.0130
Self-Pay	0.6	(0.32, 1.14)	0.1224
Other/Unknown	0.9	(0.27, 2.72)	0.7960
Cancer Type-Perceived Bleeding Risk			
High Bleed Risk-Brain	4.6	(3.74, 5.55)	<0.0001
High Bleed Risk-Acute Leukemia	0.9	(0.46, 1.61)	0.6401
Mid Bleed Risk-Kidney/Bladder	1.0	(0.85, 1.26)	0.7449
Metastatic Disease (vs. No)	1.5	(1.34, 1.62)	<0.0001
Severity of Illness (vs. Minor)			
Moderate	1.4	(1.13, 1.72)	0.0020
Major	1.9	(1.53, 2.37)	<0.0001
Extreme	1.8	(1.41, 2.41)	<0.0001
Bleeding (vs. None)			
Present on Admission	2.7	(2.09, 3.50)	<0.0001
Hospital Acquired	2.7	(1.94, 3.88)	<0.0001
Bleeding Type (vs. Other/Transfusion)			
ICH	2.2	(1.09, 4.51)	0.0285
GI	1.5	(1.09, 2.03)	0.0123
Thrombolytic Agent (vs. None)	1.4	(1.01, 2.02)	0.0452
Major Surgery (vs. None)	4.9	(3.89, 6.14)	<0.0001
Prior Surgery (vs. None)			
Prior Surgery- <7 days	0.8	(0.52, 1.26)	0.3587
Prior Surgery- 8-60 days	1.0	(0.87, 1.12)	0.8248
Vascular Surgery (vs None)	1.5	(1.00, 2.15)	0.0524
Comorbidities (vs. None)			
1-2 Comorbidity	1.2	(1.04, 1.42)	0.0126
3+ Comorbidities	1.5	(1.25, 1.74)	<0.0001
VTE Type (vs. PE)			
Proximal DVT	1.4	(1.28, 1.57)	<0.0001
Distal DVT	1.5	(1.33, 1.71)	<0.0001
Facility Size (vs. 200+ beds)			
0-99 beds	0.4	(0.26, 0.50)	<0.0001
100-199 beds	0.9	(0.76, 0.98)	0.0280
Type of Facility (vs. Kaiser)			
Private	1.8	(1.59, 2.10)	<0.0001
Teaching	1.5	(1.24, 1.76)	<0.0001
Location of Facility (vs. Urban)			
Rural	0.4	(0.25, 0.52)	<0.0001
Kind of Facility (vs Non-Profit)			
For Profit	0.9	(0.81, 1.01)	0.0791

NH = Non-Hispanic; PE = Pulmonary Embolism; DVT = Deep Vein Thrombosis; ICH = Intracranial hemorrhage.
Reprinted with permission [24].

placement in these patients, despite lack of contraindication to anticoagulation in most, may reflect an overall perception that brain tumors have a higher propensity for intracranial hemorrhage while on anticoagulation. While brain tumors are highly vascular, retrospective studies have suggested the actual risk of intracranial bleeding while on anticoagulation in patients with primary brain tumors is not significantly increased [38-40]. Several studies have also revealed high rates of complications with IVCF use in brain tumor patients [41,42]. One study found that in 42 patients treated with IVCFs, 62% developed complications including recurrent PE and DVT, filter thrombosis and post-thrombophlebitis syndrome. Interestingly, none of the patients who received both anticoagulation and IVCF had hemorrhagic complications in this report [43]. In addition, a recent retrospective study showed that anticoagulation with low molecular weight heparin in patients with metastatic brain tumors was not associated with increased risk of central nervous system hemorrhage [44]. Despite the overall evidence showing a low rate of intracranial hemorrhage and a high risk of complications related to IVCF use, the present study reveals IVCFs are frequently used in brain cancer patients.

The use of IVCFs to treat VTE in patients, both in those with cancer and without cancer, continues to be controversial. A few single center studies have found that IVCFs are safe and highly effective in preventing PE-related deaths in patients with both hematological and solid tumors [23,27]. However, other studies found increased rates of IVCF-related complications in cancer patients including new vena cava thrombosis, retroperitoneal hemorrhage, recurrent VTE and mal-deployed filters, and have questioned the benefit of IVCF placement in patients with advanced malignancy [22,23,40,45]. Several studies have also reported that in patients with stage III and IV malignant disease, IVCF placement conferred no survival benefit compared to treatment with anticoagulation therapy [45,46]. The cost-effectiveness of IVCFs in cancer patients has also been questioned [47,48].

In this large cohort of hospitalized patients with acute VTE and an active cancer, IVCF treatment showed no benefit for short-term mortality and no reduction in recurrent VTE manifested as PE (+/- DVT). Additionally, we found a 60% increased risk of recurrent VTE manifested as DVT and 20% increased risk of subsequent bleeding when an IVCF was placed. It should be noted these findings were in models adjusted for the presence of significant clinical bleeding.

In contrast to our findings, a recent retrospective study showed a decreased case-fatality rate in a subset of cancer patients hospitalized for pulmonary embolism [49]. Stable patients (without shock, ventilatory support, thrombolytic therapy, or pulmonary embolectomy) with pulmonary embolism and cancer at discharge from short-stay hospitals in the United States from were identified from the Nationwide Inpatient Sample. In-hospital all-cause case fatality rate was lower with vena cava filters in stable patients with pulmonary embolism and solid malignant tumors providing they were aged >30 years, but there was variability according to type of tumor and age of patient. On average, case fatality rate among those >30 years with filters was 7070 of 69,350 (10.2%) (95% confidence interval, 10.0-10.4) versus 36,875 of 247,125 (14.9%) (95% confidence interval, 14.8-15.1) without filters (P<0.0001) (relative risk 0.68). Interestingly, in stable patients with hematological malignancies, case fatality rate, except in the elderly, was higher among those with vena cava filters than those without filters. They speculated that this might be due to overall poorer condition of these patients, but they were unable to adjust for severity of illness. The analysis also did not adjust for potential confounders for mortality using multivariable models nor propensity scoring to adjust for the differences in the group receiving IVCF versus those that did not.

Despite the lack of demonstrated benefit, cancer patients hospitalized with acute VTE are almost two times more likely to have a IVCF placed in comparison to non-cancer patients [10]. The clinical variables most strongly associated with IVCF placement in cancer patients were active bleeding, undergoing a major operation, presence of metastatic disease, greater severity-of-illness at the time of admission, and presence of comorbidities. However, overall only 21% of those who had an IVCF placed had active bleeding or

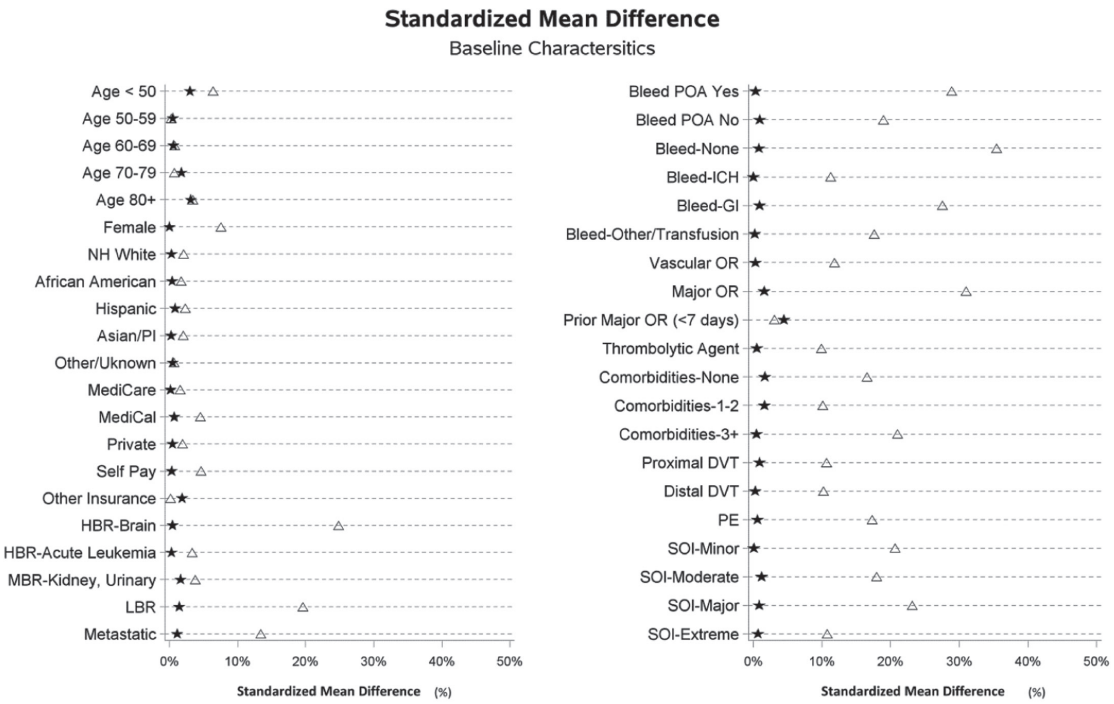

Fig. 4. Effect of inverse propensity weighting on standardized mean differences. HBR, MBR, LBR = high-, mid-, low-bleed risk group; SOI = severity of illness.

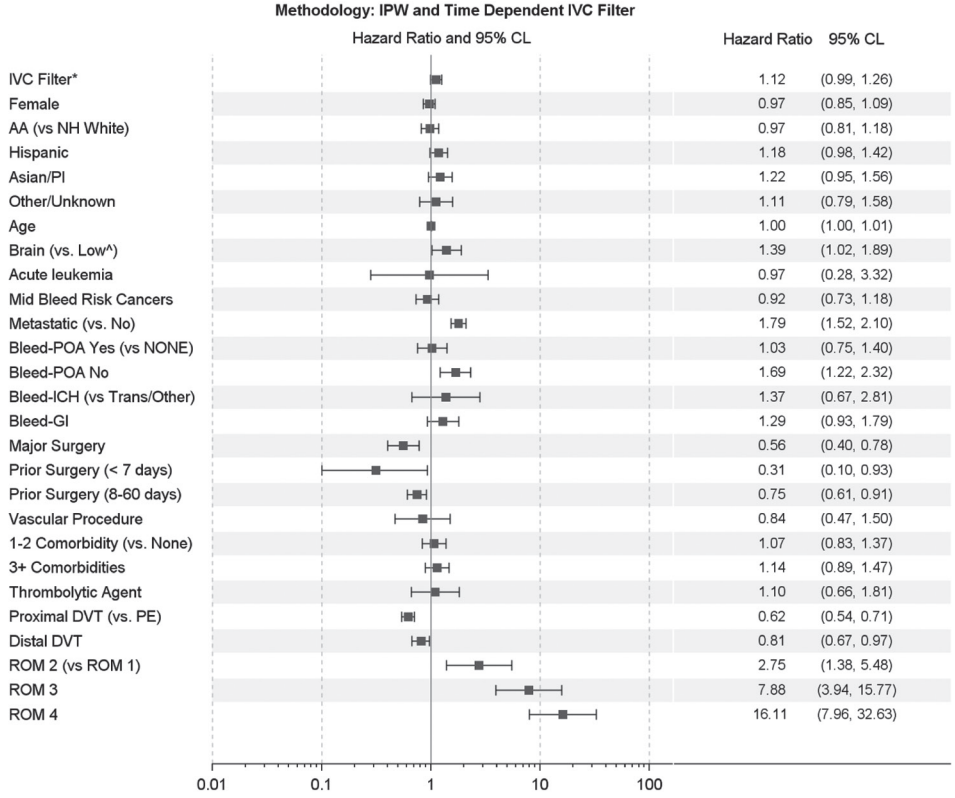

Fig. 5. Death ≤30 days. * Time dependent IVC filter placement; ^ Cancer category is based on bleed risk. ROM = risk of mortality score.

underwent major surgery. Therefore, only a minority of the cancer patients with IVCF had a clear contraindication to anticoagulation.

There are a number of limitations to these observational data. There was minimal information on cancer stage (other than metastatic cancer) or cancer therapy. Future studies may determine the effect of these clinical variables on the frequency of IVCF placement. There was not reliable data on whether retrievable IVCFs were used, and if so whether the filter was retrieved. While it is possible that hospitals that place IVCFs in a large proportion of cancer patients with acute VTE do actually remove the IVCF within a short period of time, current literature suggests that only a small proportion of retrievable VCFs are actually retrieved [9,50].

Due to the retrospective nature of the study, it is possible that more patients may have had a contraindication to anticoagulation than

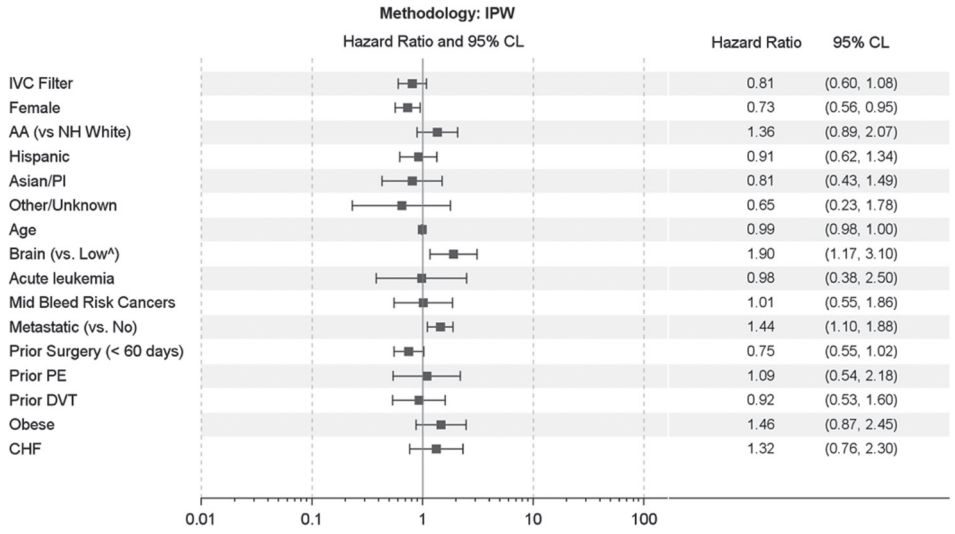

Fig. 6. Subsequent PE (+/- DVT) at ≤180 days. ^ Cancer category is based on bleed risk.

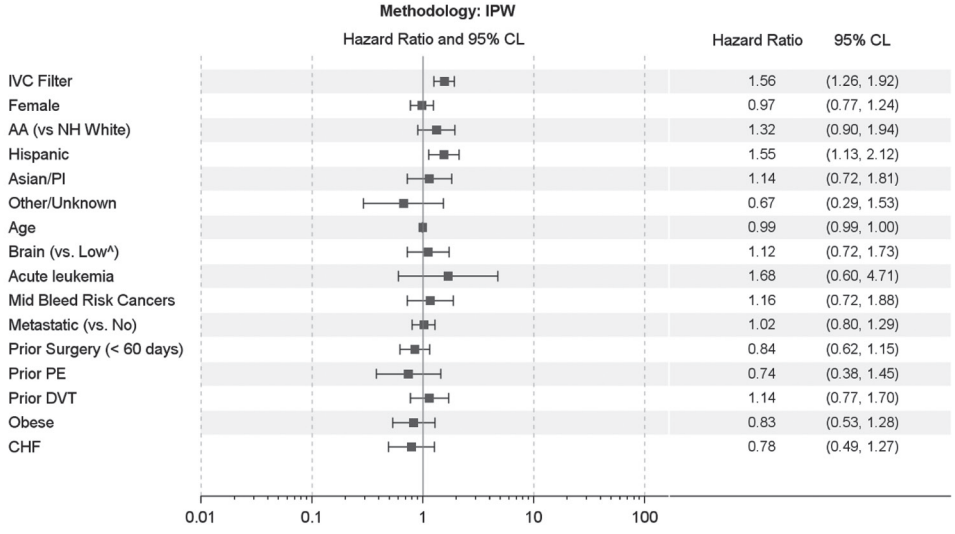

Fig. 7. Subsequent DVT at ≤180 days. ^ Cancer category is based on bleed risk.

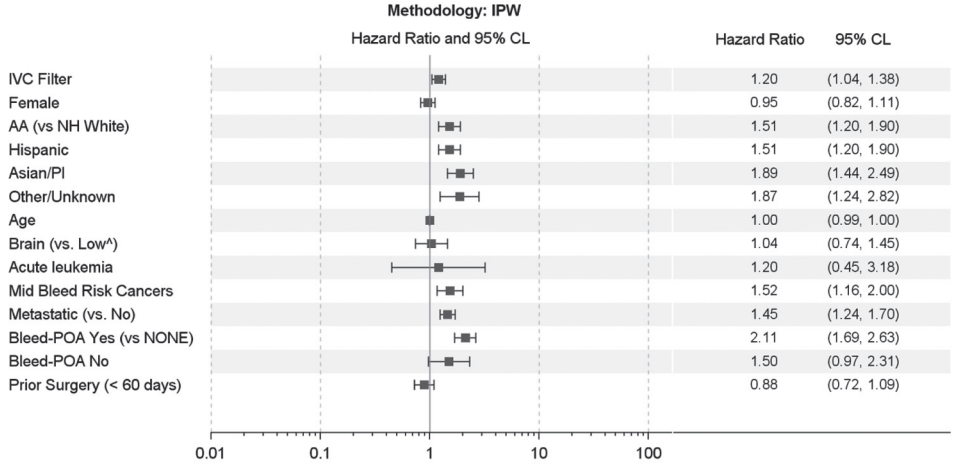

Fig. 8. Subsequent bleed at ≤180 days. ^ Cancer category is based on bleed risk.

observed. While we could not identify the specific clinical indication for placement of each IVCF, we did adjust for contraindications to anticoagulation, such as bleeding and undergoing surgery during the hospitalization. While we could not directly determine whether bleeding occurred prior to filter placement, we included both those with bleeding on admission and during the hospitalization in our study cohort. This may mean that even fewer patients actually had active bleeding and a true contraindication to anticoagulation requiring filter placement when initially diagnosed with VTE. We could not identify specific attending physicians or their specialty.

There may be as much between-physician variation in VCF use within each hospital as there is variation between hospitals. Thus, the observed degree of variation in IVCF use among hospitals may underestimate even larger variations among physician-groups both within and between hospitals.

Despite the limitations, this work has several strengths. The database used includes all inpatient and emergency department admissions to all non-federal hospitals in California and results likely reflect the "real-world". We used propensity score methodology to balance our treatment groups to the extent possible in an observational study. IVCF was treated as a time dependent covariate to help eliminate the immortal time bias in the IVCF treatment group.

Conclusions

We observed large variation between hospitals and cancer types in the frequency of IVCF use in patients with cancer. Most patients with cancer that had VCF placement did not have clear contraindications to anticoagulation.

In this large retrospective observational study that adjusted for immortal time bias and propensity weighted methodology to adjust for differences between those that received and did not receive an IVCF, there was no benefit to filter insertion. We found no improvement in short-term mortality and no reduction in recurrent PE (within 180 days). Our results demonstrated more harm than benefit, with a 56% increase in recurrent DVT as well as a 20% increase in subsequent bleeding among patients treated with an IVCF. Our study results do not support the systematic use of IVCF treatment in cancer patients with acute VTE.

Conflict of Interest

The authors report no relevant conflicts of interest.

Acknowledgements

GW was supported by an HONORS Award from the American Society of Hematology; RHW is supported by the Hibbard Williams Endowed Chair; TW is supported by TR000002 from NCATS, NIH.

This work has be presented, in part, at the International Conference on Thrombosis and Hemostasis in Cancer, Bergamo, Italy, May 2014, the American Society of Hematology Annual Meeting, San Francisco, CA, USA December 2014 and the International Society for Hemostasis and Thrombosis, Toronto, CN, July 2015.

References

[1] Girard P, Meyer G, Parent F, Mismetti P. Medical literature, vena cava filters and evidence of efficacy. A descriptive review. Thromb Haemost. 2014;111(4):761-9.
[2] Prasad V, Rho J, Cifu A. The inferior vena cava filter: how could a medical device be so well accepted without any evidence of efficacy? JAMA Intern Med. 2013;173(7):493-5; discussion 5.
[3] Group PS. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation. 2005;112(3):416-22.
[4] Nicholson W, Nicholson WJ, Tolerico P, Taylor B, Solomon S, Schryver T, et al. Prevalence of fracture and fragment embolization of Bard retrievable vena cava filters and clinical implications including cardiac perforation and tamponade. Archives of internal medicine. 2010;170(20):1827-31.
[5] White RH, Zhou H, Kim J, Romano PS. A population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. Archives of internal medicine. 2000;160(13):2033-41.
[6] Wittenberg G, Kueppers V, Tschammler A, Scheppach W, Kenn W, Hahn D. Long-term results of vena cava filters: experiences with the LGM and the Titanium Greenfield devices. Cardiovasc Intervent Radiol. 1998;21(3):225-9.
[7] Rajasekhar A, Streiff MB. Vena cava filters for management of venous thromboembolism: a clinical review. Blood Rev. 2013;27(5):225-41.
[8] Malek JY, Kwolek CJ, Conrad MF, Patel VI, Watkins MT, Lancaster RT, et al. Presentation and treatment outcomes of patients with symptomatic inferior vena cava filters. Ann Vasc Surg. 2013;27(1):84-8.
[9] Administration UFaD. Removing Retrievable Inferior Vena Cava Filters: Initial Communication 2010 [cited 2011 Aug 16]. Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm221676.htm.
[10] White RH, Geraghty EM, Brunson A, Murine S, Wun T, Spencer F, et al. High Variation Between Hospitals in Vena Cava Filter Use for Venous Thromboembolism. JAMA Internal Medicine. 2013.
[11] Stein PD, Kayali F, Olson RE. Twenty-one-year trends in the use of inferior vena cava filters. Archives of internal medicine. 2004;164(14):1541-5.
[12] Mismetti P, Laporte S, Pellerin O, Ennezat PV, Couturaud F, Elias A, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA : the journal of the American Medical Association. 2015;313(16):1627-35.
[13] Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-94S.
[14] Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. Journal of thrombosis and haemostasis : JTH. 2013;11(1):71-80.
[15] Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA : the journal of the American Medical Association. 2005;293(6):715-22.
[16] Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer. 2013;49(6):1404-13.
[17] Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-8.
[18] Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine. 1999;78(5):285-91.
[19] Gussoni G, Frasson S, La Regina M, Di Micco P, Monreal M. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. Thrombosis research. 2013;131(1):24-30.
[20] Monreal M, Falga C, Valdes M, Suarez C, Gabriel F, Tolosa C, et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. Journal of thrombosis and haemostasis : JTH. 2006;4(9):1950-6.
[21] Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Archives of internal medicine. 2006;166(4):458-64.
[22] Barginear MF, Lesser M, Akerman ML, Strakhan M, Shapira I, Bradley T, et al. Need for inferior vena cava filters in cancer patients: a surrogate marker for poor outcome. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2009;15(3):263-9.
[23] Wallace MJ, Jean JL, Gupta S, Eapen GA, Johnson MM, Ahrar K, et al. Use of inferior vena caval filters and survival in patients with malignancy. Cancer. 2004;101(8):1902-7.
[24] Ho G, Brunson A, White R, Wun T. Vena cava filter use in cancer patients with acute venous thromboembolism in California. Thrombosis research. 2015;135(5):809-15.
[25] Grannis SJ, J.M. O, McDonald CJ. Analysis of identifier performance using a deterministic linkage algorithm. Proceedings / Amia Symposium. 2002:305-9.
[26] Hser Y, Evans E. Cross-system data linkage for treatment outcome evaluation: lessons learned from the California Treatment Outcome Project. Evaluation and Program Planning. 2008(31):2.
[27] Athanasoulis CA, Kaufman JA, Halpern EF, Waltman AC, Geller SC, Fan C-M. Inferior Vena Caval Filters: Review of a 26-year Single-Center Clinical Experience1. Radiology. 2000;216(1):54-66.
[28] Stein PD, Matta F, Hull RD. Increasing Use of Vena Cava Filters for Prevention of Pulmonary Embolism. The American Journal of Medicine. 2011;124(7):655-61.
[29] Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401.
[30] Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med. 2009;151(5):297-305.
[31] Elixhauser. Comorbidity software 2011. Available from: http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp.
[32] Schoenman JA, Sutton JP, Elixhauser A, Love D. Understanding and Enhancing the Value of Hospital Discharge Data. Medical Care Research and Review. 2007;64(4):449-68.

[33] Lavernia CJ, Laoruengthana A, Contreras JS, Rossi MD. All-Patient Refined Diagnosis-Related Groups in Primary Arthroplasty. The Journal of Arthroplasty. 2009;24(6, Supplement):19-23.
[34] Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33(7):1242-58.
[35] Liu J, Weinhandl ED, Gilbertson DT, Collins AJ, St Peter WL. Issues regarding 'immortal time' in the analysis of the treatment effects in observational studies. Kidney Int. 2012;81(4):341-50.
[36] Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of Guarantee-Time Bias. Journal of Clinical Oncology. 2013;31(23):2963-+.
[37] Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. Brit Med J. 2010;340.
[38] Choucair AK, Silver P, Levin VA. Risk of intracranial hemorrhage in glioma patients receiving anticoagulant therapy for venous thromboembolism. Journal of neurosurgery. 1987;66(3):357-8.
[39] Altschuler EM, Jungreis CA, Sekhar LN, Jannetta PJ, Sheptak PE. Operative treatment of intracranial epidermoid cysts and cholesterol granulomas: report of 21 cases. Neurosurgery. 1990;26(4):606-13; discussion 14.
[40] Olin JW, Young JR, Graor RA, Ruschhaupt WF, Beven EG, Bay JW. Treatment of deep vein thrombosis and pulmonary emboli in patients with primary and metastatic brain tumors. Anticoagulants or inferior vena cava filter? Archives of internal medicine. 1987;147(12):2177-9.
[41] Lee AY, Levine MN. Management of venous thromboembolism in cancer patients. Oncology (Williston Park). 2000;14(3):409-17, 21; discussion 22, 25-6.
[42] Schwarz RE, Marrero AM, Conlon KC, Burt M. Inferior vena cava filters in cancer patients: indications and outcome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1996;14(2):652-7.
[43] Levin JM, Schiff D, Loeffler JS, Fine HA, Black PM, Wen PY. Complications of therapy for venous thromboembolic disease in patients with brain tumors. Neurology. 1993;43(6):1111-4.
[44] Donato J, Campigotto F, Uhlmann EJ, Coletti E, Neuberg D, Weber GM, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. Blood. 2015;126(4):494-9.
[45] Schunn C, Schunn GB, Hobbs G, Vona-Davis LC, Waheed U. Inferior vena cava filter placement in late-stage cancer. Vascular and endovascular surgery. 2006;40(4):287-94.
[46] Ihnat DM, Mills JL, Hughes JD, Gentile AT, Berman SS, Westerband A. Treatment of patients with venous thromboembolism and malignant disease: should vena cava filter placement be routine? Journal of vascular surgery. 1998;28(5):800-7.
[47] Jarrett BP, Dougherty MJ, Calligaro KD. Inferior vena cava filters in malignant disease. Journal of vascular surgery. 2002;36(4):704-7.
[48] Chau Q, Cantor SB, Caramel E, Hicks M, Kurtin D, Grover T, et al. Cost-effectiveness of the bird's nest filter for preventing pulmonary embolism among patients with malignant brain tumors and deep venous thrombosis of the lower extremities. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2003;11(12):795-9.
[49] Stein PD, Matta F, Sabra MJ. Case fatality rate with vena cava filters in hospitalized stable patients with cancer and pulmonary embolism. Am J Med. 2013;126(9):819-24.
[50] Duszak Jr R, Parker L, Levin DC, Rao VM. Placement and Removal of Inferior Vena Cava Filters: National Trends in the Medicare Population. Journal of the American College of Radiology. 2011;8(7):483-9.