

Rates of Venous Thromboembolism Among Patients with Major Surgery for Cancer

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ABSTRACT

Background. Previous studies have reported VTE rates during surgical stays in hospitals or by diagnoses over extended periods without being linked to specific surgical events. The purpose of this project was to assess the potential rate of venous thromboembolism in patients with cancer after a surgical procedure within the immediate posthospital admission period of 30 days, with special emphasis in increased sensitivity of detection.

Methods. Patients with cancer who had a major surgery were identified in a large commercial (non-Medicare) database containing data from more than 22 million patients in the United States. Those with a new diagnosis of VTE within 30 days postadmission for surgery were identified. Additional drug-based criteria were used to vary the VTE definition in a sensitivity analysis. VTE rates are reported for each of the surgical procedure group and overall.

Results. The overall 30-day VTE rate was 3.5% with a diagnosis based definition, with rates ranging by procedure from 1.8 to 13.2%. Esophageal resection patients have a VTE rate of 13.2% (95% confidence interval (CI), 8.8–18.9%), whereas prostatectomy patients have a VTE rate of 1.8% (95% CI, 1.5–2.1%). Of the 3.5% of patients with a VTE diagnosis on or before postoperative day 30, 73% of those have the VTE diagnosis by day 14. Another 1.15% is added to the overall VTE rate as the definition sensitivity is increased with outpatient pharmacy claims data.

Conclusions. Using administrative data from large populations provides valuable insight into the potential VTE rates that occur within the 30-day post period after various cancer-related surgeries. The information can be used by surgeons as one component of the benefit-risk decision regarding postoperative VTE prophylaxis in surgical patients.

Since at least the mid 1960s, the number of patients in the United States with venous thromboembolism (VTE) has been increasing, causing a major national health problem.¹ For the purposes of this study VTE refers to both deep vein thrombosis (DVT) and pulmonary embolism (PE) events. A considerable volume of research has described the underlying rate of VTE based on various risk factors. In the U.S. population, annual incidence rates have been reported from 43.7 to 145 per 100,000.² Douketis et al. have shown that the risk of VTE is higher in patients with cancer, chronic cardiovascular disease, chronic respiratory disease, and other clinically significant medical disease with odd ratios ranging from 1.79 to 2.72.³ Edelsberg et al. reported that patients with a history of cancer, history of VTE, operating room procedure 30 days or less before their admission, peripheral artery disease, or heart failure also have a higher hazard of VTE when admitted to the hospital (hazard ratios ranging from 6.14 to 1.67).⁴ Other factors that have been suggested as risk factors for developing VTE include: surgery, trauma, cardiac or respiratory failure, lower extremity paralysis, hip fracture, prior VTE, increased age, and immobility.⁵ Despite all of this research, a limited number of reports describe the VTE rate within the immediate postoperative period after a surgical procedure for cancer.

VTE rates have been estimated for some specific types of surgical procedures in various populations; however, the length of the postoperative period was not consistent across these studies. Cardiothoracic, abdominal, and major

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orthopedic surgeries have shown significant risks.⁵ Sweetland et al. confirmed this finding, showing variation by surgery type, with risk of VTE increasing during the first 3 weeks after surgery for cancer or hip or knee replacement.⁶ In total knee arthroplasty in a population of Australian patients, the in-hospital VTE incidence was 3.9% (95% confidence interval (CI), 2.2–6.8%) (variable duration hospitalizations) and 5.7% at 3 months (95% CI, 1.6–18.6%).⁷ Rasmussen et al. reported that the incidence of overall VTE after major abdominal or pelvic surgery was 14.3% (95% CI, 11.2–17.8%) in the control group and 6.3% (95% CI, 4–8.7%) for patients receiving out-of-hospital low molecular weight heparin within 3 months of surgery.⁸ However, studies did not typically report rates across a wide variety of surgical procedures using a standard global postoperative interval, such as 30 days.

The American College of Chest Physicians has promulgated evidence-based VTE guidelines since the late 1980s.⁹ In a joint statement released in 2009, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO), the Italian Association of Medical Oncology (AIOM), and the French National Federation of the League of Centers Against Cancer (FNCLCC) published guidelines regarding VTE prophylaxis in patients with cancer.¹⁰ All of the groups agreed that low molecular weight heparins are preferred for the treatment of patients with VTE in cancer; however, they called for sustained research to investigate clinical issues such as “Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?” NCCN recommends that cancer patients undergoing surgery should receive risk-stratified prophylaxis, yet clear agreement on risk stratification methods has not been reached. Lifetime or long interval VTE rate by some cancer sites have been published but not by each surgical event.^{11,12} VTE rates by selected cancer site included pancreas 8.1%, kidney 5.6%, and lung 5.1%, but these are not postoperative rates.¹⁰ A postoperative VTE rate would need to be known to make recommendations regarding the benefit of perioperative prophylaxis associated with a specific surgical procedure for a specific patient.

Therefore, a gap exists in the current literature regarding rates of VTE within a fixed length (30-day) postoperative period for specific surgeries, including VTE rates in cancer patients who are already at a high risk of VTE.

In an effort to address this unmet need, this study presents results of an analysis of postoperative (within 30 days) venous thromboembolism (VTE) rates after major surgery in cancer patients. The data were derived from a large commercially insured administrative database. Surgeries included in this analysis represent major abdominal, pelvic, retroperitoneal, and (noncardiac) thoracic surgery in cancer patients.

METHODS

The study methodology allowed for multiple levels of increasing sensitivity in the VTE definition using an additive approach that allows the researcher to make assumptions about the likelihood of VTE being present. The core definition of a VTE was the ICD-9 CM diagnosis code. The additional three expanding levels of VTE definition were based on classes of prescription medications to create *upper boundaries* of VTE presence identifying additional potential VTE cases.

Data Source

The data are administrative claims from a large insurer and contain all of the information that will appear on a HCFA 1,500 professional claim form or UB-92 facility claim form (summary charge data). All outpatient prescriptions are available as well as medications billed under HCPCS codes. All outpatient diagnoses are available as well as the top inpatient diagnoses. The i3 InVision Data Mart™, a large National administrative claims database represents an employed, commercially insured population with dependents with approximately 22 million lives. The database was available from 1 October 2005 through 31 March 2009 and included member, medical, and outpatient pharmacy data. This database was chosen due to the volume of patients available and the ability to follow patients after discharge from the hospital.

Study Design

This was a retrospective analysis of administrative healthcare data. Patient confidentiality was assured by the data supplier in compliance with all HIPPA regulations.

Study Period

A 180-day period before the admission date was used to establish preexisting conditions and comorbidities. Patients with preexisting VTE were not excluded. VTE was identified from the hospital admission date plus 14 days and admission date plus 30 days. Although the rate is referred to as being 30 days postoperative, it is technically 30 days after admission. The time from admission to surgery is not available in the administrative data.

Surgeries of Interest

Patients were identified if they had a claim with a procedure code for major abdominal, pelvic, retroperitoneal, and (noncardiac) thoracic surgical procedure from 1 April 2006 through 28 February 2009. The ICD9 procedure

codes that were used to identify surgical hospitalizations are presented in Table 1.

Study Population

Inclusion Criteria Patients were included in the study if they met all of the following criteria:

- Had a primary inpatient procedure code for one of the selected open surgical procedures (Table 1) between 1 April 2006 and 28 February 2009
- Were continuously eligible for 180 days or longer before the day of the first qualifying procedure (i.e., index date)
- Had at least one diagnosis during the 180-day preperiod of cancer (ICD-9-CM 140.XX to 239.XX)

Exclusion Criteria • Younger than 21 years of age

- Presence of an alcohol or substance abuse diagnosis (ICD-9-CM diagnosis codes 303.xx, 304.xx, and 305.xx (excluding 305.1x))
- Presence of a pregnancy diagnosis (ICD-9-CM codes 630.xx - 679.xx and V22.xx and V22.xx)

Outcome Definition

The primary analysis variable was an indicator variable for presence of VTE. As an indicator variable, it was designed to have high sensitivity. The primary definition (Definition 1) of VTE was based on presence of the ICD-9-CM diagnosis codes presented in Table 2 or presence of a procedure code indicating a claim for a inferior vena cava (IVC) filter (HCPCS code C1880 or CPT codes 37620 or 75940). This definition is similar to the PSI-12, an indicator established in 2006 by the Agency for Healthcare Research and Quality to monitor VTE rates at the provider level during hospital admissions using administrative claims data. VTE Indicator variables were developed for presence of each of these codes in the 30 days after admission for surgery (inclusive of the day of the admission).

In the event that the VTE diagnosis was not recorded in the administrative data (VTE definition 1), a sensitivity analyses was conducted using index drugs (i.e., those that were potentially or likely used to treat a new VTE event) as indicators of patients that might have a VTE not documented in the dataset. With each definition, the sensitivity to detect VTE increases. These four definitions represent four hierarchical criteria used to define a potential VTE cases. Although it is recognized that these definitions were broader than VTE, they were used as surrogates for a recorded diagnosis code of VTE and to establish an upper bound. Drugs were identified using American Hospital

Formulary Service (AHFS) generic product identifier (GPI) code or brand names.

VTE definition 2 is the presence of definition 1 or a warfarin prescription (GPI class = M9L) during the post-period where there was no indication during the 180 days preoperative and where there was no diagnosis of atrial fibrillation (ICD-9-CM = 427.31) in the 210-day study period. VTE definition 3 is the presence of definition 2 or any heparin-like anticoagulant prescription (GPI class = M9K) that was not present during the 180 days preoperative period and where there was no diagnosis of atrial fibrillation (ICD-9-CM = 427.31) during the 210-day study period. The category includes low molecular weight heparins, such as dalteparin sodium, enoxaparin (Lovenox), and fondaparinux sodium heparin sodium. Definition 4 is the presence of definition 3 or a platelet aggregation inhibitor prescription (GPI class = M9P) during the postperiod that was not present during the 180 days preoperative and where there was no diagnosis of atrial fibrillation (ICD-9-CM = 427.31) during the 210-day study period. This platelet aggregation inhibitor category includes cilostazol, clopidogrel bisulfate, dipyridamole, and ticlopidine HCl (aspirin/extended-release dipyridamole combination).

Analysis Plan

The number and percentage of patients with an indication of VTE as defined by the four definitions by day 30 after admission is presented overall and by surgery type. Clopper-Pearson confidence intervals (95%) were calculated.

RESULTS

There were 44,130 patients in the database who had at least one code for a surgical procedure of interest. After applying the inclusion and exclusion criteria, the final sample consisted of 20,762 patients with a mean age of 58.3 years (SD 9.9) and was 69.5% male and 30.5% female. The anatomical region of the surgery was 42% abdominal, 38% pelvic, 16% retroperitoneal, and 4% (noncardiac) thoracic. The distribution of surgical procedures that qualified the patients for the analysis is shown in Fig. 1.

The 30-day postoperative VTE rate, using definition 1, in the overall cancer patient sample is 3.5% (95% CI, 3.2–3.7). The VTE rates vary by the type of surgery performed is shown in Fig. 2 and reported in Table 3. Esophageal resection patients have a VTE rate of 13.2% (95% CI, 8.8–18.9%), whereas prostatectomy patients have a VTE rate of 1.8% (95% CI, 1.5–2.1%). The confidence interval for the VTE rate in each surgery type is a reflection of the number of those surgeries in the sample. Prostatectomy and

TABLE 1 Surgical codes used for selecting the sample of patients with an open abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgical procedure

Procedure	ICD 9 procedure codes	Description
Pulmonary resection	32.39 ^a	Other and unspecified segmental resection of lung
	32.49 ^a	Other lobectomy of lung
	32.59 ^a	Other and unspecified pneumonectomy
	32.6	Radical dissection of thoracic structures
Pancreaticoduodenectomy, radical	52.7	Radical pancreaticoduodenectomy
Nephrectomy, radical	55.51	Nephroureterectomy
	55.69	Other kidney transplantation
Prostatectomy	60.5	Radical prostatectomy
	60.4	Retropubic prostatectomy
Colectomy c/s anal anastomoses	45.61	Multiple segmental resection of small intestine
	45.71	Open and other multiple segmental resection of large intestine
	45.73	Open and other right hemicolectomy
	45.74	Open and other resection of transverse colon
	45.75	Open and other left hemicolectomy
	45.76	Open and other sigmoidectomy
	45.79	Other and unspecified partial excision of large intestine
	45.8 ^b	Total intra-abdominal colectomy
	45.82 ^c	Open total intra-abdominal colectomy
	45.83 ^c	Other and unspecified total intra-abdominal colectomy
	42.41	Partial esophagectomy
Esophageal resection	42.42	Total esophagectomy
	42.52	Intrathoracic esophagogastrostomy
	42.55	Intrathoracic esophageal anastomosis with interposition of colon
	42.55	Intrathoracic esophageal anastomosis with interposition of colon
Abdominoperineal resection	48.5 ^b	Abdominoperineal resection of rectum
	48.5 ^c	Abdominoperineal resection of the rectum, not otherwise specified
	48.52 ^c	Open abdominoperineal resection of the rectum
	48.59 ^c	Other abdominoperineal resection of the rectum
Cystectomy, radical	57.6	Partial cystectomy
	57.71	Radical cystectomy
	57.79	Other total cystectomy
Pancreatectomy	52.52	Distal pancreatectomy
	52.53	Radical subtotal pancreatectomy
	52.59	Other partial pancreatectomy
	52.6	Total pancreatectomy
Nephrectomy, partial	55.4	Partial nephrectomy
Gastrectomy	43.5	Partial gastrectomy with anastomosis to esophagus
	43.6	Partial gastrectomy with anastomosis to duodenum
	43.7	Partial gastrectomy with anastomosis to jejunum
	43.89	Other partial gastrectomy
	43.91	Total gastrectomy with intestinal interposition
	43.99	Other total gastrectomy
Low anterior resection	48.62	Anterior resection of rectum with synchronous colostomy
	48.63	Other anterior resection of rectum

TABLE 1 continued

	Procedure	ICD 9 procedure codes	Description
	Other	50.22	Partial hepatectomy
^a Codes that were not active until October 2007		50.3	Lobectomy of liver
		50.4	Total hepatectomy
^b Codes that were replaced October 2008		40.52	Radical excision of periaortic lymph nodes
		40.53	Radical excision of iliac lymph nodes
^c Codes that were not active until October 2008		59	Retroperitoneal dissection, not otherwise specified

TABLE 2 ICD-9-CM codes used for identification of VTE events (definition 1)

ICD-9-CM	Description
415.19	Other pulmonary embolism and infarction
451.11	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
451.19	Phlebitis and thrombophlebitis of other
451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.81	Phlebitis and thrombophlebitis of iliac vein
451.83	Phlebitis and thrombophlebitis of deep veins of upper extremities
451.9	Phlebitis and thrombophlebitis of unspecified site
453.2	Embolism and thrombosis of inferior vena cava
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.8 ^a	Acute venous embolism and thrombosis of other specified veins
453.9	Embolism and thrombosis of unspecified site
HCPCS	Description
C1880	Vena cava filter
CPT	Description
37620	Interruption, partial or complete, of inferior vena cava by suture, ligation, plication, clip, extravascular, intravascular (umbrella device)
75940	Percutaneous placement of IVC filter, radiological supervision and interpretation

^a A fifth digit was added in October 2009 and was not available for the study period

colectomy were the most frequent surgeries, hence the narrower confidence intervals. Esophageal resection and abdominoperineal resection were the least frequent procedures, hence the wide confidence interval for the VTE rate.

The percent of surgical cancer patients who have a VTE diagnosis code (definition 1) on or before day 14 after the surgical admission (vs. day 30) also was calculated. Of the 3.5% of patients with a VTE diagnosis on or before day 30, 73% of those have the VTE diagnosis by day 14 after surgery (14-day rate is 2.5%; 95% CI, 2.3–2.7%). The 14-day VTE rate in the various surgeries range from 58 to 86% of the 30-day rate.

Figure 3 illustrates the potential incremental increase above the diagnosis-based VTE rate using the three

additional definitions based on use of outpatient anticoagulant regimens. In the overall group, the upper bound of VTE cases is increased from the 3.5% of patients meeting definition 1, by an additional 0.26, 0.7, and 0.19% as definitions 2, 3, and 4 are added until an upper bound of 4.61% is reached. Confidence intervals are not shown in Fig. 3 to reduce the complexity of the graph; however, the relative size of the confidence intervals will be similar to those in Fig. 2 because the frequency of each surgery is the primary factor that influences the magnitude of the confidence interval. It is noteworthy that there is substantial variation among the different surgery types with regard to the likelihood that additional patients were detected using definitions 2 through 4.

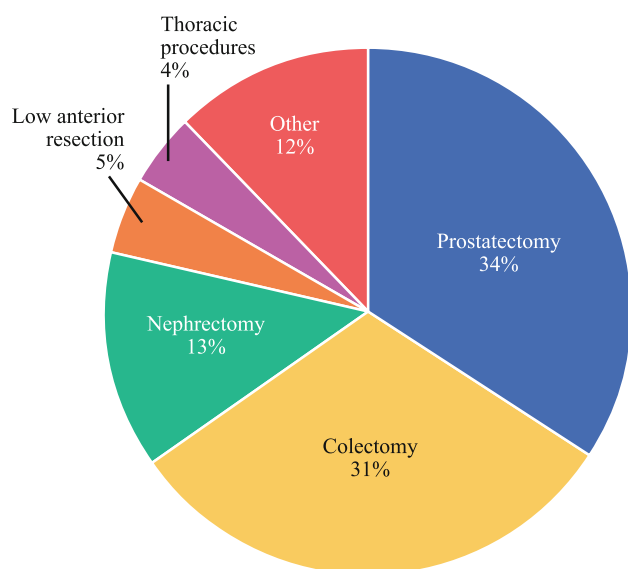


FIG. 1 Distribution cancer patients by surgical procedure ($n = 20,762$)

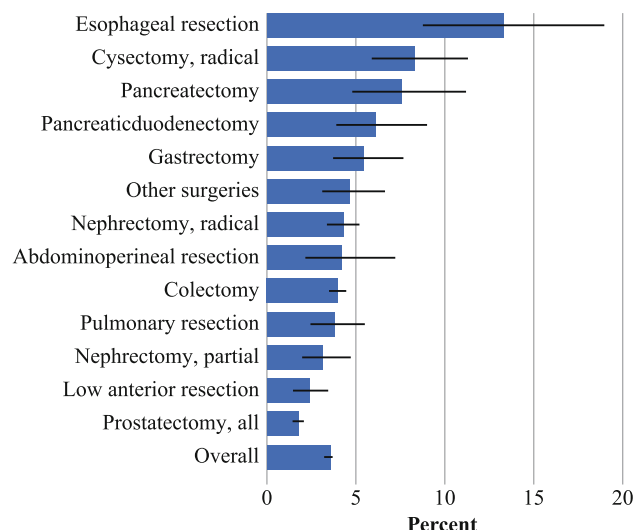


FIG. 2 VTE rate and confidence interval in 13 selected categories of surgical procedures in patients with cancer. (VTE rate was defined by definition 1, which included one of the diagnostic codes listed in Table 2)

DISCUSSION

While it was generally understood that cancer patients are at a higher risk of VTE, for a variety of reasons, the risk of VTE within the 30-day postoperative period has not been previously reported by the type of surgery over a broad range of procedures. The range of risk by surgery within the 30-day postoperative period also has not been reported. The range from the lowest to the highest rate is more than a factor of 7 (1.8–13.2%) in the surgeries studied. Based on this information, surgeons may choose to

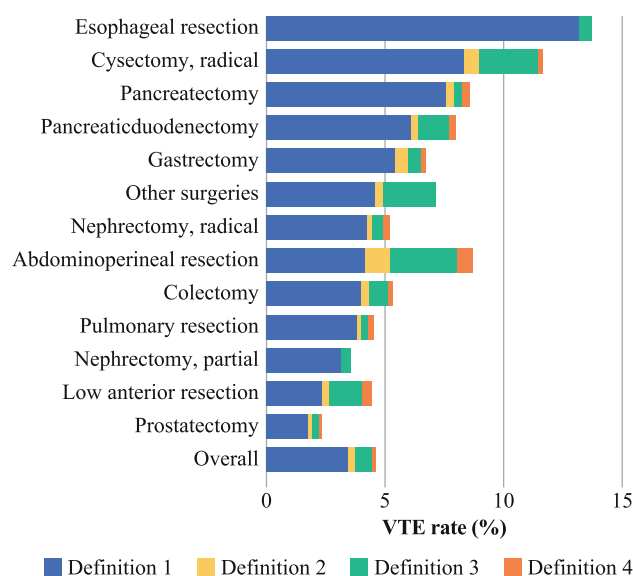


FIG. 3 VTE rate by surgical procedure and definition in 13 selected categories of surgical procedures in patients with cancer. (VTE rate was defined using the definitions described in Table 3)

use these VTE rates as one component of their risk-benefit analysis of peri- and postoperative VTE prophylaxis.

A quality measure proposed by AHRQ, Patient Safety Indicator #12 (PSI-12), is similar to definition 1; however, the PSI #12 indicator is limited to the length of the hospital stay. The PSI-12 is being used as a quality measure to compare surgeons or hospitals. Although it is possible to adjust the PSI-12 by the DRG-mix using an AHRQ-supplied beta coefficient, it may be better to report the PSI-12 rate relative to the expected rate observed in each population. For example, if a surgeon has a mix of 50% gastrectomy procedures (VTE rate of 5.6%) and 50% colectomy procedures (VTE rate of 3.9%), the expected VTE rate would be 4.75%. The surgeon's or hospital's observed PSI-12 score or VTE rate and its confidence interval can then be compared to the weighted VTE rate based on this research to determine if the observed rate is significantly different than what would be expected due to chance alone.

The prescription products used as VTE indicators in definitions 2, 3, and 4 may be used as treatment for a confirmed VTE, for prophylaxis of VTE, or for another indication. Based on the information provided on an outpatient prescription claim, it is not possible to determine whether the intended use is for treatment or prophylaxis. The use must be considered to interpret properly these measures, which are reported here to represent an upper bound. The large variation in the percentage of patients who satisfy definitions 2–4 by surgery type may indicate that the rate of outpatient prophylaxis or treatment varies

TABLE 3 VTE rate and confidence interval in 13 selected categories of surgical procedures in patients with cancer ($n = 20,762$)

Surgery	# VTE cases	%	Clopper–Pearson CI	
			Low (%)	High (%)
Pulmonary resection	27	3.8	2.5	5.5
Pancreaticoduodenectomy, radical	23	6.1	3.9	9
Nephrectomy, radical	87	4.3	3.4	5.2
Prostatectomy, radical or simple	126	1.8	1.5	2.1
Colectomy c/s anal anastomoses	257	4	3.5	4.5
Esophageal resection	25	13.2	8.8	18.9
Abdominoperineal resection	12	4.2	2.2	7.2
Cystectomy, radical	37	8.3	5.9	11.3
Pancreatectomy	22	7.6	4.8	11.2
Nephrectomy, partial	23	3.1	2	4.7
Gastrectomy	30	5.4	3.7	7.7
Low anterior resection	23	2.4	1.5	3.5
Other surgeries ^a	27	4.6	3.1	6.6
Overall 30-day	719	3.5	3.2	3.7
Overall 14-day	523	2.5	2.3	2.7

VTE rate was defined by definition 1, which included one of the diagnostic codes listed in Table 2

^a Now includes retroperitoneal

considerably by the type of surgical procedure performed and not necessarily by the risk of VTE.

Future research can potentially use other pharmacy and medical claims to report chemotherapy use, a risk factor in developing VTE. If the claims data have sufficient clinical details indicating reasons for CT or duplex, these services may be useful to potentially identify VTE patients.

A limitation of this analysis (and any analysis of administrative claims data) is that the comparability of the definition of VTE between administrative data and a clinically confirmed diagnosis is not established within this study. A frequently cited study notes that the degree of concordance between claims data in general and clinically confirmed diagnoses can be low.¹³ However, misclassification was lower for surgical encounters than for medical encounters. In the current study, a sensitivity analysis around the diagnosis-based definition (definition 1) using outpatient prescription claims (definitions 2–4) was used to partially address this issue. In a comparison of administrative data diagnoses versus medical chart review, the rate of VTE reported by administrative data is higher; however, neither was validated against direct patient observation of the VTE by objective assessment.¹⁴

In using these VTE rates as a source of comparison or benchmarking to other VTE rates from other sources, it is important to remember that there were many variables that were not controlled, such as type of medical care facility, geographic region, age and gender distributions of the surgical patients, etc. (Patients older than age 65 years who

were covered by Medicare exclusively are not included in this database.) The results in this report will need to be interpreted in light of this limitation.

The fact that there is a wide variation of VTE rates by procedure would indicate that a risk-based algorithm for prophylaxis (as recommended by ASCO) is warranted. The rates from this research may form a foundation for such an algorithm combined with patient-specific factors. Future research can focus on the validation of diagnosis-based VTE definitions relative to objective assessment.

CONCLUSIONS

Postoperative VTE rates within the standard 30-day global postoperative period for a broad range of major surgical procedures have not been previously reported and could be useful to surgeons as part of their decision-making regarding the benefits and risks of VTE prophylaxis. The method employed in this research, which takes advantage of large sample sizes from administrative data, may be useful for this informational purpose. Although it is known that VTE rates are higher in patients with cancer, the magnitude of the increased VTE rate and the variation between types of cancer surgeries may be different than what was previously reported. Because these rates are based on diagnosis codes in the administrative data, and have not been validated using VTE diagnostic tests, additional clinical research is needed to corroborate these findings.

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