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Venous Thromboembolic Events Following Major Pelvic and Abdominal Surgeries for Cancer: A Prospective Cohort Study

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ABSTRACT

Objective. The aim of this study was to evaluate the incidence and risk factors for post-hospital discharge venous thromboembolism (VTE) following abdominal cancer surgery without post-discharge prophylaxis.

Methods. This was a single-center, prospective cohort study. Patients were evaluated at 1, 3, and 6 months from surgery for the presence of proximal deep vein thrombosis (DVT; screening ultrasound at 1 month and questionnaire at each visit). Cumulative VTE incidence with 95% confidence interval (CI) was estimated using Kaplan–Meier methods, and multivariable analysis was performed using a Cox proportional hazards model.

Results. Of 284 patients enrolled, 79 (28%) underwent colorectal laparotomy, 97 (34%) underwent hepatobiliary laparotomy, 100 (35%) underwent gynecological laparotomy, and 8 (3%) underwent exploratory laparotomy without resection. All patients received pre- and postoperative inpatient prophylaxis. The cumulative incidence of VTE at 1 month was 0.35% (95% CI 0.05–2.48), 2.5% at 3 months (95% CI 1.19–5.15), and 7.2% at 6 months (95% CI 4.72–10.97). Screening ultrasound performed 4 weeks after surgery in 50% of patients was negative for thrombosis in all cases. Event distribution was similar according to the type of surgery (open/laparoscopic) and type of cancer. Seventeen (6.6%) patients died (95% CI 3.5–9.4) (two had a VTE-related death). Postoperative chemotherapy and Caprini score were significantly associated with VTE [hazard ratios 3.77 (95% CI 1.56–9.12) and 1.17 (95% CI 1.02–1.34), respectively].

Conclusion. The incidence of post-hospital discharge proximal DVT and/or symptomatic VTE following abdominal and pelvic cancer surgery appears to be low. The cumulative number of events increased at 6 months, but this was likely due to additional risk factors that were not related to surgery. Postoperative chemotherapy increases the risk of VTE.

Venous thromboembolism (VTE), manifested by deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious complication that occurs after abdominal operations.[1,2] Patients with cancer are at increased risk of developing VTE.[3] Proposed mechanisms for increased risk include overexpression of tissue factor, increased platelet activation by cancer procoagulant proteins, oversecretion of cytokines, and chemotherapy.[4] Surgery further increases risk due to tissue trauma and postoperative immobility. The incidence of postoperative in-hospital and outpatient VTE rates has been reported to be 10–40%.[2,5–7] Randomized

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trials and prospective cohort studies have proven perioperative administration of low-dose heparin to be effective in preventing postoperative VTE.[1,2,8–10]

Prolonged VTE prophylaxis for 4 weeks after abdominal cancer surgery with low-molecular-weight heparin (LMWH) has been studied in randomized trials, demonstrating a substantial reduction in the incidence of VTE at 3 months following cancer surgery (relative risk 0.21, 95% confidence interval [CI] 0.05–0.94),[11] and has also been studied in a number of meta-analyses and clinical practice guidelines.[1] These guidelines propose that standard prophylactic regimens should be tailored according to individual patient risk factors as a result of the lack of prospective data on laparoscopic procedures and patients enrolled in 'enhanced recovery after surgery' pathways.[12–17] Perceived limitations of the trial methodology, e.g. open-label design as a source of bias, low incidence of events with venography as a surrogate outcome for VTE, and concerns with generalizability resulting from the limited number of hepatobiliary and gynecological procedures, are other considerations that have precluded broader implementation.[1,13–15,18]

Given the current lack of clarity on the incidence of VTE in these specific patient populations, we conducted a study to determine the incidence of VTE within 6 months following surgery and to investigate risk factors associated with its occurrence.

METHODS

Participants

We performed a prospective, single-center, cohort study of consecutive patients aged ≥ 40 years, undergoing elective open or laparoscopic major abdominal or pelvic operations for cancer from the gastrointestinal tract (other than esophagus), hepatobiliary, or gynecological system. Exclusion criteria included evidence of VTE during the previous 3 months, ongoing treatment with anticoagulant agents, and patients who experienced major postoperative hemorrhage who did not receive in-hospital prophylaxis. Patients were enrolled prior to surgery, and received preoperative and postoperative in-hospital VTE prophylaxis. Institutional ethics approval was obtained prior to commencement, and written informed consent was obtained from all participants included in the study.

Outcomes

The primary outcome was VTE, either proximal DVT (popliteal veins and above) or PE, at 1 month following discharge. Compression ultrasound (CUS) was performed using a high-resolution 7.5 MHz linear-array transducer. The deep veins were evaluated for compressibility at 1 cm intervals from the common femoral vein to the popliteal vein. PE was defined by an intraluminal filling defect on spiral computed tomography (CT). Other sites of VTE included the upper extremities (basilic, brachial, axillary, subclavian, and internal jugular veins), confirmed by CUS; inferior vena cava, renal vein or splanchnic vein thrombosis (portal, gastric, splenic, inferior mesenteric, superior mesenteric, or suprahepatic veins and branches), diagnosed by CT or ultrasound; or VTE-related death (autopsy-proven PE, DVT, or splanchnic vein thrombosis). The definition for postoperative major bleeding can be found elsewhere.[19] Based on this definition, we included intraoperative bleeding as a component of postoperative bleed in order to have a more general idea of the process, even though no study medications were administered before or after surgery.

Risk Factors for Venous Thromboembolism (VTE)

Demographic characteristics, tumor location, and clinical risk factors for VTE at baseline were collected and classified using the Caprini Score, a validated risk assessment tool for surgical patients.[20] These factors included age, prior major surgery, inflammatory disease, obesity, sepsis, serious lung and heart disease, history of VTE, and family history of VTE. Information on the type of cancer, type of surgical procedure performed, bleeding complications, transfusion rate, duration of surgery, length of hospital stay, and administration of pre- and postoperative chemotherapy (including type and duration) was also recorded.

Follow-Up

Participants were followed for 6 months after index operation. Asymptomatic patients were offered a CUS of the lower extremities 4 weeks postoperatively. Patients were interviewed by a research assistant at 1, 3, and 6 months to evaluate for the presence of VTE, cancer recurrence, and receipt of chemotherapy. Clinically suspected VTE cases were assessed according to local practice standards as determined by the treating physician. All screening CUSs of the lower extremities were performed and read by experienced radiologists. Death and the cause of death were confirmed from hospital records, the treating or family physician, or family members.

Data were reported and collected prospectively from hospital records, clinic and office charts, laboratory notes, and patient questionnaires. Source documentation was required for each outcome reported and reviewed by an

adjudication committee consisting of two experienced physicians, with any disagreement resolved by consensus.

Statistical Analysis

The sample size was calculated to achieve a desired precision of 95% CI width of 0.1 around the estimated VTE rate at 1 month. Assuming the VTE rate at 1 month was 7%, 140 patients undergoing CUS were required to achieve the desired precision. The cumulative incidence of VTE was estimated using Kaplan–Meier methods. The association between VTE and five prespecified risk factors, determined a priori, were assessed using the Cox proportional hazards model. Exploratory multivariable analyses were performed for the individual components of the Caprini score. All p values were two-sided, with values < 0.05 considered to be statistically significant. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA) and R 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria).[21]

RESULTS

From January 2015 to February 2016, 357 eligible patients were screened, of whom 284 were enrolled in the study. The most common reasons for exclusion was the absence of cancer on final pathology ($n = 31$) and the requirement for anticoagulation therapy at discharge ($n = 28$) because of atrial fibrillation or previous VTE (Fig. 1). Of the patients enrolled, 142 (50%) underwent a screening CUS. Baseline characteristics were similar between patients who did and did not undergo screening CUS (electronic supplementary Table 2). Patients who did not undergo screening CUS were followed prospectively and were included in the final analysis. All patients were followed for 6 months after index surgery or until death, and were included in the primary outcome analysis. No patients were lost to follow-up.

Baseline characteristics, operative details, and other risk factors for VTE, including the use of preoperative and postoperative chemotherapy, are reported in Table 1. In summary, there were 79 (28%) colorectal patients, 97 (34%) hepatobiliary patients, 100 (35%) gynecological patients, and 8 (3%) patients who underwent exploratory laparotomies without resections. Overall, 71 (25%) patients underwent laparoscopic surgery, with the type of surgery (open and laparoscopic) evenly distributed among subspecialties: 33% colorectal patients, 21% hepatobiliary patients, and 23% gynecological patients.

All patients received preoperative VTE prophylaxis, most with unfractionated heparin (99%). In the postoperative in-hospital period, all patients received VTE prophylaxis, mostly with LMWH (88%). No patients received prolonged VTE prophylaxis following hospital discharge. Intraoperative and predischarge major bleeding was observed in 118/284 (42%) patients. Packed red blood cells were transfused to 54 (20%) patients intraoperatively and 24 (9%) patients postoperatively. Postoperative chemotherapy was administered to 104 (37%) patients during the 6-month study timeframe.

Incidence of VTE

Over the 6-month follow-up period, 20 patients experienced VTE after discharge: 3 patients with lower extremity proximal DVT, 8 with PE, 5 with upper extremity vein thrombosis, 2 with splanchnic vein thrombosis, and 2 with renal vein thrombosis. The cumulative incidence of VTE at 1 and 3 months was 0.35% (95% CI 0.05–2.48) and 2.5% (95% CI 1.19–5.15), respectively, while the cumulative incidence at 6 months was 7.2% (95% CI 4.72–10.97) (Fig. 2). The hazard rates for the time intervals of 0–1 month, 1–3 months, and 3–6 months were 0.0001 (1 VTE), 0.0004 (6 VTEs), and 0.0006 (13 VTEs), respectively. All CUSs performed at 1 month among asymptomatic patients in the cohort ($n = 142$) were negative. Events were similarly distributed according to the type of surgery: 7.6% colorectal, 6.2% hepatobiliary, and 8% gynecology. Events were similar in laparoscopic or open surgery: 7% VTE in the laparoscopic group and 7% in the open group.

All events except one (renal vein thrombosis) were considered clinically significant and treated with anticoagulation. Most events were symptomatic (17/20). Three patients had asymptomatic PE diagnosed on follow-up cancer staging CT scans. Four of the five cases with upper extremity DVT had central venous catheters. There were 17 deaths in the cohort (6.6, 95% CI 3.5–9.4), of which five were preceded by VTE, and two VTE-related deaths, both splanchnic vein thrombosis (Table 2).

Factors Associated with VTE

Factors associated with VTE were Caprini score (hazard ratio [HR] 1.17, 95% CI 1.02–1.34) and postoperative chemotherapy (HR 3.77, 95% CI 1.56–9.12). Other factors such as length of hospital stay, presence of metastases, or preoperative chemotherapy were not found to be associated with VTE (Table 3). Of the 20 patients with VTE, 14 (70%) received postoperative chemotherapy; all 14 events occurred while patients were receiving chemotherapy (Table 2).

Components of the Caprini score that were associated with a higher rate of VTE in the multivariable analysis were previous myocardial infarction (odds ratio [OR] 4.8,

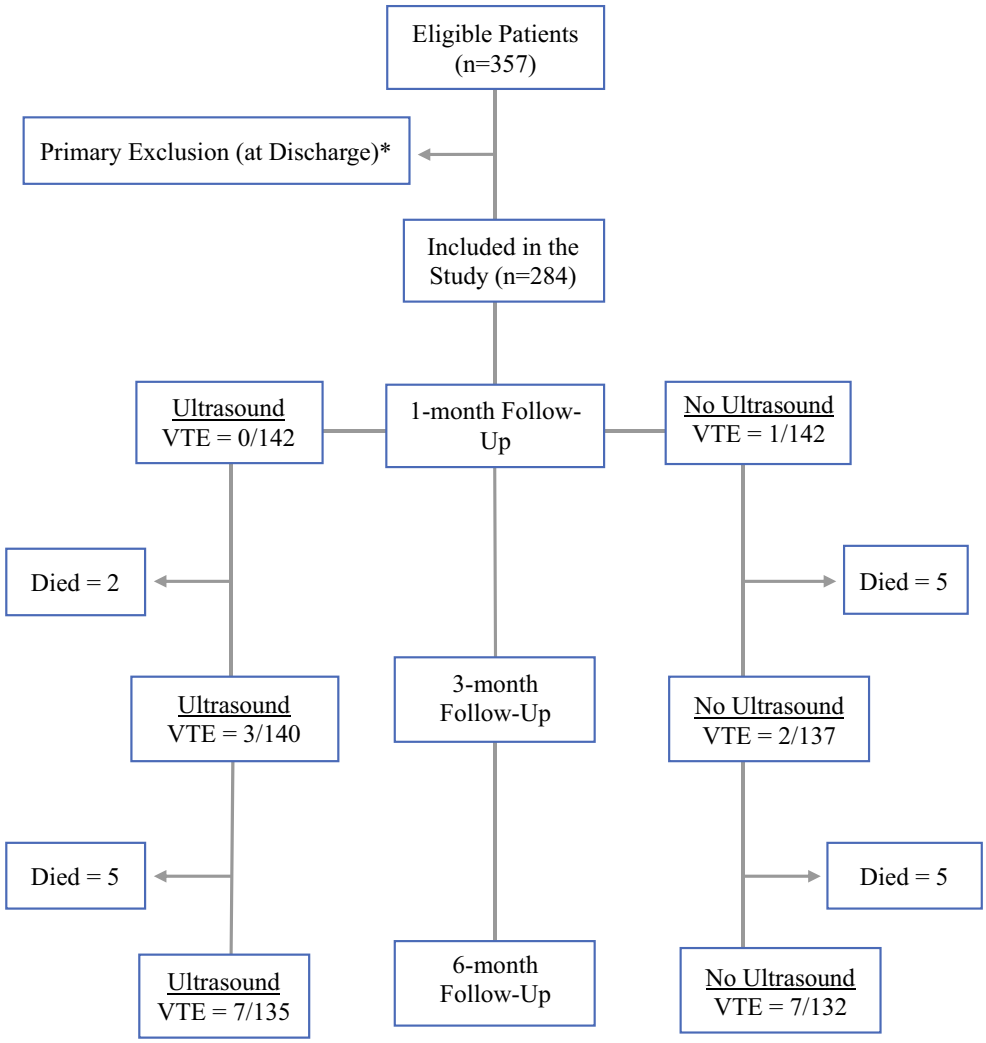

FIG. 1 Consort flow diagram depicting patients participating in the study. Follow-up refers to the time from index operation. *Reasons for primary exclusion at discharge from the hospital were final pathology not being cancer (31 patients; 7 colorectal, 5 hepatobiliary, 19 gynecology); not discharged within 28 days (3 patients); surgery cancelled (1 patient); prescribed anticoagulation upon discharge from the hospital (28 patients; 6 prior anticoagulation treatment, 4 previous VTEs considered at high risk and treated with anticoagulation, 15 atrial fibrilation, 1 participant in a clinical trial comparing placebo versus anticoagulation for acute coronary event, 2 in-hospital VTEs); death during hospital stay (8 patients); language barrier (1 patient), and dementia (1 patient). *VTE* venous thromboembolic events

95% CI 3.1–6.4), central venous catheters (OR 3.0, 95% CI 2.0–4.0), postoperative blood transfusions (OR 2.3, 95% CI 1.4–3.3), patients aged ≥ 75 years (OR 2.3, 95% CI 1.4–3.3), and surgery lasting more than 3 h (OR 4.6, 95% CI 3.3–5.8) [electronic supplementary Table 1].

DISCUSSION

In this study, the incidence of VTE following discharge at 1 month after surgery was much lower than expected (< 1%). The incidence of VTE increased between 3 and 6 months after surgery. These findings contrast with the higher incidence of VTE found at 1 month (12% all VTEs, 2% symptomatic VTE) and 3 months (14% all VTEs, 4% symptomatic VTE) in the placebo group in the ENOXACAN-II study, which evaluated the use of enoxaparin versus placebo for a duration of 21 days following surgery.[14] Similarly, in the CANBESURE study (comparing bemiparin with placebo for 28 days following surgery), the rate of all VTEs in the placebo group at 1 month after surgery was 10.3%, and the rate of symptomatic VTE was 3.3%. In the CANBESURE study, similar rates were found 3 months from surgery.[15] The discrepancy between the incidence of VTE and the ratio of asymptomatic/symptomatic VTEs in our study versus the ENOXACAN-II and CANBESURE studies is likely related, in part, to the method of diagnosing and screening for VTE. In these studies, patients were screened using venography, and both proximal and distal DVTs were included, with the majority of events being distal asymptomatic VTEs.[14, 15]

TABLE 1 Baseline characteristics and type of surgery

Characteristic	Patients [*N* = 284]
Sex	
Male	113 (40)
Female	171 (60)
Age, years [median (range)]	66 (40–90)
BMI [median (range)]	27 (15–63)
Tumor location	
Colon	65 (23)
Rectum	45 (16)
Endometrium	53 (19)
Ovarian	39 (14)
Pancreas	27 (13)
Preoperative chemotherapy	65 (23)
Prior VTE	7 (3)
Central venous catheter	130 (46)
OR type	
Hepatectomy	43 (15)
Pancreatectomy	44 (16)
Colectomy	49 (17)
Proctectomy	23 (8)
Gynecological surgery	100 (35)
Postoperative bleeding	118 (42)
Duration of surgery, min [median (range)]	197 (55–762)
Intraoperative blood transfusions	54 (20)
Postoperative blood transfusions	24 (9)
LOS [median (range)]	5 (1–42)
Postoperative chemotherapy	104 (37)
Minimally invasive surgery	71 (25)

Data are expressed as *n* (%) unless otherwise specified

VTE venous thromboembolic event, *BMI* body mass index, *LOS* length of hospital stay

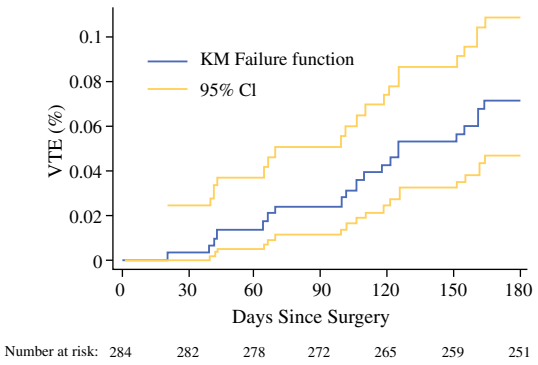

FIG. 2 Kaplan–Meier failure function with 95% confidence interval. *VTE* venous thromboembolic events, *KM* Kaplan–Meier, *CI* confidence interval

In our cohort, the majority of events happened between the third and sixth month following surgery, which was not observed in prior studies. Our study included one-third of hepatobiliary patients and one-third of gynecology patients, of whom 20–30% were laparoscopic cases. Compared with prior studies, that included no hepatobiliary procedures and a small number of gynecological procedures or laparoscopic cases. In our study, most patients were enrolled in an 'enhanced recovery after surgery' pathway, which was not available when prior studies were conducted. Patients enrolled in this pathway are thought to have a lower incidence of post-hospital discharge VTE, mostly due to a shorter hospital stay.[22] Also in our study, patients at higher risk of developing VTE, including those with prior diagnosis of VTE, who were given VTE prophylaxis following discharge, were excluded from the study ($n = 4$). In contrast to other studies, our cohort considered events as all cases of venous thrombosis, including splanchnic vein thrombosis and renal vein thrombosis. The effect of short-term or long-term VTE prophylaxis in patients with these types of events is unknown as it is thought to be associated more with surgical technical issues. Therefore, by eliminating these events, the incidence of VTE in our cohort would be even lower.

Factors in the Caprini score were found to be significant for the development of VTE after hospital discharge. These factors were grouped in this score, given the small number of events and the fact that this score has been widely validated. When analyzing the factors associated with VTE, it is clear that postoperative chemotherapy, regardless of the timing of administration after surgery, is associated with a higher risk of VTE. Chemotherapy as a risk factor for VTE has previously been extensively investigated, with proposed mechanisms including direct damage to the vascular endothelium, increasing levels of procoagulant molecules, and reducing anticoagulant molecules.[23] Chemotherapy also increases platelet activation and induces overexpression of tissue factor in monocytes, similar to the overstimulation seen with cancer.[24,25] It is therefore expected that patients receiving postoperative chemotherapy are at higher risk of VTE.

Our study demonstrates that the incidence of VTE continues to rise up to 6 months following surgery. Prior studies have suggested a lower risk of VTE up to 3 months with the use of prolonged VTE prophylaxis following hospital discharge.[14,15] It is unclear if the administration of prolonged VTE prophylaxis for a total of 4 weeks following surgery has any effect on the risk of VTE at 6 months. Most of the events in our cohort occurred between the third and sixth month following surgery, while patients were receiving chemotherapy.

TABLE 2 Distribution and type of event

Time to event (days)	Location	Symptomatic/ asymptomatic	Postoperative chemotherapy	Chemotherapy type	Death (cause)
22	Iliac vein	Symptomatic	N	N	Y (CA progression)
41	Lung	Symptomatic	Y	Letrozole	N
42	Internal jugular	Symptomatic	N	N	N
43	Lung	Symptomatic	N	N	Y (CA progression)
64	Basilic vein	Symptomatic	Y	Gemcitabine	N
66	Lung	Asymptomatic	Y	FOLFOX	N
70	Subclavian	Symptomatic	Y	FOLFOX	N
100	Renal	Symptomatic	Y	Y	N
102	Lung	Asymptomatic	Y	FOLFOX	N
106	Renal	Symptomatic	N	N	N
113	Portal	Symptomatic	N	N	Y (SVT)
119	Trifurcation	Symptomatic	Y	Carbo/Taxol	N
124	Portal	Symptomatic	N	N	Y (SVT)
126	Femoral	Symptomatic	Y	FOLFOX	N
127	Subclavian	Symptomatic	Y	Cisplatin/Taxol	N
152	Lung and bilateral leg	Asymptomatic	Y	Carbo/Taxol	Y (CA progression)
156	Lung	Symptomatic	Y	FOLFIRI with bevacizumab	N
161	Lung	Symptomatic	Y	Carbo/Taxol	N
162	Basilic	Symptomatic	Y	Cisplatin/Taxol	N
165	Lung	Symptomatic	Y	Carbo/Taxol	N

Time to event in days indicates time from index surgery

Chemotherapy indicates postoperative chemotherapy only

Y yes, *N* no, *CA* cancer, *SVT* superficial vein thrombosis, *FOLFOX* combination chemotherapy fluorouracil, leucovorin and oxaliplatin, *FOLFIRI* folinic acid, fluorouracil and irinotecan, *TAXOL* paclitaxel, *CARBO* carboplatin

TABLE 3 Multivariable analysis for delayed post-discharge venous thromboembolic events (Cox proportional hazards model)

Variable	VTE [*n* = 20]	No VTE [*n* = 264]	HR	95% CI	*p* value
Caprini score [median (range)]	12 (7–16)	11 (4–24)	1.17	1.02–1.34	0.039
Postoperative chemotherapy [*n* (%)]					
No	8 (40)	172 (65)	3.77	1.56–9.12	0.003
Yes	12 (60)	92 (35)			
LOS [median (range)]	6 (1–25)	5 (0–42)	1.03	0.99–1.08	0.174
Metastases [*n* (%)]					
No	14 (70)	190 (72)	1.10	0.41–2.97	0.850
Yes	6 (30)	74 (28)			
Preoperative chemotherapy [*n* (%)]					
No	17 (85)	199 (76)	0.58	0.17–1.96	0.381
Yes	3 (15)	62 (24)			

VTE venous thromboembolic events, *LOS* length of hospital stay, *HR* hazard ratio, *CI* confidence interval

Limitations of our study include the relatively small sample, the highly selected group of patients, which may limit its generalizability, and the low number of events, which potentially decreases the sensitivity of our statistical regression analysis to detect VTE risk factors. In our study, we only used CUS to screen for proximal DVT. Although

CUS is less sensitive than venography for detecting asymptomatic distal vein thrombosis, a few distal vein thrombi may have been missed in our study.

Approximately 50% of patients did not undergo screening CUS as patients were reluctant to travel to the study center for a visit not related to the management of their cancer; however, we do not feel that this impacts on the validity of our results. First, none of the patients in the non-CUS group were lost to follow-up; hence, clinical follow-up can be considered a surrogate for the occurrence of VTE. Second, the baseline characteristics and risk of VTE for the CUS and non-CUS cohorts were similar. Third, in the CUS group, the DVT rate at 4 weeks was lower than the rate in the non-CUS group. It is possible that failure to detect DVT at 1 month may, in part, explain the late VTEs, but only a small part. If venography was performed 1-month post-surgery, a few asymptomatic distal VTEs would have been detected, however these would not have been detected by screening CUS. They would most likely have to extend proximally to be detected by CUS.

CONCLUSIONS

Our prospective cohort evaluating the incidence of post-hospital discharge proximal DVT and/or symptomatic VTE following major pelvic and abdominal cancer surgery demonstrated that the incidence of VTE is relatively low in relationship to other studies, even without extended thromboprophylaxis. The cumulative number of events increased at 6 months, but this was likely due to additional risk factors not related to surgery.

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CONFLICT OF INTEREST Pablo E. Serrano, Sameer Parpia, Lori-Ann Linkins, Laurie Elit, Marko Simunovic, Leyo Ruo, Mohit Bhandari, and Mark Levine report no conflicts of interest.

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