ORIGINAL ARTICLE

Observational Study

Colectomy is a risk factor for venous thromboembolism in ulcerative colitis

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Abstract

AIM: To compare venous thromboembolism (VTE) in hospitalized ulcerative colitis (UC) patients who respond to medical management to patients requiring colectomy.

METHODS: Population-based surveillance from 1997 to 2009 was used to identify all adults admitted to hospital for a flare of UC and those patients who underwent colectomy. All medical charts were reviewed to confirm the diagnosis and extract clinically relevant information. UC patients were stratified by: (1) responsive to inpatient medical therapy (n = 382); (2) medically refractory requiring emergent colectomy (n = 309); and (3) elective colectomy (n = 329). The primary outcome was the development of VTE during hospitalization or within 6 mo of discharge. Heparin prophylaxis to prevent VTE was assessed. Logistic regression analysis determined the effect of disease course (*i.e.*, responsive to medical therapy, medically refractory, and elective colectomy) on VTE after adjusting for confounders including age, sex, smoking, disease activity, comorbidities, extent of disease, and IBD medications (*i.e.*, corticosteroids, mesalamine, azathioprine, and infliximab). Point estimates were presented as odds ratios (OR) with 95%CI.

RESULTS: The prevalence of VTE among patients with UC who responded to medical therapy was 1.3% and only 16% of these patients received heparin

prophylaxis. In contrast, VTE was higher among patients who underwent an emergent (8.7%) and elective (4.9%) colectomy, despite greater than 90% of patients receiving postoperative heparin prophylaxis. The most common site of VTE was intra-abdominal (45.8%) followed by lower extremity (19.6%). VTE was diagnosed after discharge from hospital in 16.7% of cases. Elective (adjusted OR = 3.69; 95%CI: 1.30-10.44) and emergent colectomy (adjusted OR = 5.28; 95%CI: 1.93-14.45) were significant risk factors for VTE as compared to medically responsive UC patients. Furthermore, the odds of a VTE significantly increased across time (adjusted OR = 1.10; 95%CI: 1.01-1.20). Age, sex, comorbidities, disease extent, disease activity, smoking, corticosteroids, mesalamine, azathioprine, and infliximab were not independently associated with the development of VTE.

CONCLUSION: VTE was associated with colectomy, particularly, among UC patients who failed medical management. VTE prophylaxis may not be sufficient to prevent VTE in patients undergoing colectomy.

Key words: Inflammatory bowel diseases; Ulcerative colitis; Deep vein thrombosis; Pulmonary embolism; Surgery

Core tip: The occurrence of venous thromboembolism (VTE) in our population-based cohort was about 5%, which highlights the importance of this complication among hospitalized ulcerative colitis (UC) patients. However, the risk of VTE was low (about 1%) among flaring ulcerative colitis patients who responded to medical management. In contrast, UC patients who underwent an elective (5%) or emergent colectomy (8.7%) had higher occurrence of VTE. After adjusting for covariates the leading risk factor for VTE was the need for colectomy. VTE occurred in colectomy patients despite > 90% postoperative VTE prophylaxis. Thus, heparin prophylaxis may not be sufficient to prevent VTE in patients undergoing colectomy.

INTRODUCTION

In the western countries the prevalence of ulcerative colitis (UC) has been reported as high as 500 cases per 100000 persons[1]. Approximately, 16% of UC patients will require colectomy within the first 10 years of diagnosis; though, colectomy rates have been decreasing overtime[2,3]. Colectomy for UC has been associated with postoperative morbidity and mortality[4-6]. An important contributor to postoperative complications is the occurrence of venous thromboembolism (VTE)[7,8], VTE carries risk of significant morbidity and mortality, particularly due to pulmonary embolism[9-11].

The inflammatory bowel diseases (IBD) have been established as an independent risk factor for developing VTE as well as recurrent VTE[12,13]. In recent years, several population-based studies showed that IBD patients are at increased risk of developing VTE[7,14]. Bernstein *et al*[7] demonstrated that IBD patients have a 3-4 fold increased risk of developing a VTE requiring hospitalization. Similar rates have been described in both ambulatory and hospitalized IBD patients[12,15], while specific studies focusing on hospitalized IBD patients showed an increased risk of 1.5-2 fold compared to hospitalized non-IBD patients[16]. In a meta-analysis the risk of VTE among IBD patients was 2-fold higher than individuals without IBD[17].

Studies have also highlighted some of the potential risk factors behind the development of VTE in IBD. One study demonstrated that IBD patients experiencing an acute flare that required steroid use were associated with an over 8-fold increased risk of VTE when compared to non-IBD patients[15]. The risk of VTE in IBD was driven by disease severity with the risk steadily increasing across IBD patients in remission, in a flare managed as an outpatient, and a flare managed in-hospital[18]. Among hospitalized IBD patients risk factors for VTE included UC, advanced age, IBD-related surgery, malnutrition, and medical co-morbidities[16,19]. Further, the prevalence of VTE among asymptomatic flaring IBD patients was low, which suggests that in-hospital factors drive the development of VTE[20]. Surgery has been recognized as an important risk factor for VTE among IBD patients[21,22]. However, studies are needed to explore the impact of VTE in UC patients who respond to in-hospital medical management as compared to those who are refractory to medical management and require colectomy.

Guidelines recommend prophylaxis for VTE using anti-coagulants (*e.g.*, subcutaneous heparin) in IBD patients who have been hospitalized for a flare of disease and following surgery[23,24]. While the use of VTE prophylactic doses of heparin in UC is recognized as safe[25,26], utilization of VTE prophylaxis for hospitalized UC patients in clinical practice may be suboptimal[27,28]. In a tertiary care referral center, nearly half of UC patients admitted to medical service were not provided VTE prophylaxis as compared to over 90% who were prescribed in a surgical service[27]. However, population-based studies that include VTE prescribing practices in community and

academic hospitals have not been explored.

We designed a large population-based study to determine the rate of VTE among UC patients who underwent an emergent or elective colectomy as compared to those who responded to in-hospital medical management. Furthermore, we explored heparin utilization in clinical practice and the efficacy of VTE prophylaxis in this population.

MATERIALS AND METHODS

Data source
The Data Integration, Measurement and Reporting (DIMR) hospital discharge abstract administrative database captures all hospitalizations in the Calgary Health Zone of Alberta Health Services, Canada. The Calgary Health Zone is a population-based health authority under a public, single payer system and provides all levels of medical and surgical care to the residents of the city of Calgary and over 20 nearby smaller cities, towns, villages, and hamlets. The estimated population of the Calgary Health Zone in 2009 was 1326115. The DIMR database contains 42 diagnostic and 25 procedural coding fields. The International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was used up to 2001, while ICD-10-CA and the Canadian Classification of Health Intervention (CCI) coding have been used after 2001[29].

Study population
The DIMR administrative discharge database was used to identify all adults ($\geq$ 18 years of age) who were admitted to hospital with a diagnosis of UC (ICD-9-CM 556.X or ICD-10-CA K51.X) and underwent colectomy (ICD-9-CM: 45.7 and 45.8 or CCI: 1.NM.87, 1.NM.89, 1.NM.91, 1.NQ.89, 1. NQ. 90) between January 1st, 1997 and December 31, 2009[4]. Medical chart review confirmed all cases of UC and colectomy[29]. UC patients who underwent a colectomy were further stratified by emergent versus elective operation. An operation was defined as "elective" if the decision to operate on the UC patient was made prior to admission to hospital. In contrast, the decision for an "emergent" colectomy was determined during the hospital admission (*e.g.*, acute complication or refractory to in-hospital medical management)[4]. For a control group, we searched the administrative databases for all patients admitted to hospital from 1997 to 2009 with UC (ICD-9-CM 556.X or ICD-10-CA K51.X) coded in the primary diagnostic position and a random subset with UC coded in the second or third diagnostic position. Chart review confirmed that these patients were admitted for a flare of UC, but were discharged after responding to medical management. These patients never underwent colectomy during the course of the study period (1997 to 2009)[29].

Outcomes
The primary outcome was the development of VTE. Occurrence of VTE was defined according to anatomic location: (1) deep vein thrombosis in a limb; (2) deep vein thrombosis outside a limb including splenic, hepatic, mesenteric, renal, cephalic, subclavian, or portal vein thrombosis; and (3) pulmonary embolism, diagnosed in isolation or with a co-existing site. The diagnosis of VTE was evaluated in two settings: (1) diagnosis occurring during hospitalization; and (2) readmission to hospital for VTE within 6 mo of discharge. Readmission to hospital for VTE was included in the study population to capture VTE that developed early after admission or during in-hospital admission, but only recognized after discharge. Among UC patients who underwent an emergent colectomy, VTE were classified as preoperative or postoperative.

Variables
The primary variable of interest was the disease course, which was evaluated in 3 settings: (1) UC patients admitted to hospital for a flare of disease and discharged from hospital without colectomy after responding to medical mangement; (2) UC patients admitted to hospital for flare of UC requiring emergent colectomy; and (3) UC patients admitted to hospital for elective colectomy. The primary colectomy was recorded as the index date and no other UC-related bowel surgery was performed prior to the index date. In addition, data extracted from hospital records included: age at admission to hospital, stratified by the tercile of the entire cohort; sex; smoking status at hosptial admission (current, ex-smoker, or never smoker); disease duration (time from diagnosis of UC to admission to hospital); disease activity (> 5 stool/d and the presence of blood in stool versus $\leq$ 5 stool/d or absence of blood); extent of disease (left-sided colitis, pancolitis, or unknown); and a non-VTE in-hospital complication.

All comorbidities observed in our patients were recorded in the following groups as previously described[29]: coronary artery disease; congestive heart failure; other cardiovascular conditions (*e.g.*, arrhythmia); cancer; diabetes; gastrointestinal (*e.g.*, pancreatitis); haematological (*e.g.*, anemia); hypertension; liver disease (*e.g.,* primary sclerosing cholangitis); neurological conditions (*e.g.*, stroke); pulmonary disease (*e.g.*, asthma); renal disease (*e.g.,* dialysis); rheumatological (*e.g.*, rheumatoid arthritis); and thyroid or adrenal disease (*e.g.*, hypothyroidism). Comorbidities were classified as having 0 or $\geq$ 1 and have been validated in this population[29].

The chart reviewer determined the use (at time of admission or past history) of the following medications: mesalamine or sulfasalazine; azathioprine or 6-mercaptopurine; prednisone; and infliximab. VTE prophylaxis was evaluated for each UC patient in

the following settings: (1) in-hospital VTE prophylaxis among medically responsive UC flare patients; (2) pre- and postoperative VTE prophylaxis among UC patients who underwent emergent colectomy; and (3) postoperative VTE prophylaxis among UC patients who underwent elective colectomy. The primary medical VTE prophylaxis used was subcutaneous heparin; however, those using low molecular weight heparin were included and classified as VTE prophylaxis.

Statistical analysis

We described the occurrence of VTE stratified by disease course (*i.e.*, medically responsive to in-hospital management, emergent colectomy, and elective colectomy). For each outcome and study variable, descriptive statistics were performed using the Fisher Exact test for proportions; continuous variables were expressed as medians with interquartile ranges and compared using the Kruskal-Wallis test. Multivariate logistic regression analysis was performed to examine the association between disease course (*i.e.*, medically responsive, emergent colectomy, and elective colectomy) and VTE after adjusting for other clinical variables. Disease course and age were *a priori* forced into the regression model. The following variables were subsequently evaluated for independent effects on VTE development using the stepwise selection approach with 0.1 as the entry and exit *P* value: sex; year of admission; smoking status; comorbidities; disease duration; extent of disease; disease activity; in-hospital complication at anytime during admission (*i.e.*, pre- or postoperatively for surgical groups), but excluding VTE; and IBD-related medications (*i.e.*, mesalamine/sulfasalazine, prednisone, azathioprine/6-mercaptopurine, and infliximab) prescribed prior to admission. These variables were considered significant if the two-sided *P* value was < 0.05. We used a stepwise selection approach to adjust our model for significant variables, while optimizing the efficiency of the model by avoiding overfitting of covariates.

In a subanalysis, we compared medically responsive UC patients to UC patients who underwent an emergent colectomy (*i.e.*, elective colectomy patients were excluded). We repeated the multivariate logistic regression analysis described above, but included a variable in the model for the use of VTE prophylaxis prior to discharge (*i.e.,*medically responsive) and prior to colectomy. Second, we compared UC patients undergoing an elective colectomy to UC patients who underwent an emergent colectomy. Similarly, we included a variable in the logistic regression model that represented VTE prophylaxis for UC patients undergoing colectomy.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, United States).

Ethical considerations

The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary.

RESULTS

Between January 1st 1997 and December 31st 2009, 638 individuals with UC who underwent a colectomy (309 emergent and 329 elective) were identified. A further 382 UC patients were admitted emergently with a flare, but were discharged after responding to in-hospital medical management. The characteristics of patients with UC are presented in Table 1. The overall VTE rate was 4.7%, and 18.8% of these individuals experienced a pulmonary embolism. The most common site of VTE was intra-abdominal (45.8%) followed by lower extremity (19.6%). Table 2 describes the location of VTE.

VTE occurred in 1.3% of medically responsive, 8.7% of emergent colectomy, and 4.9% of elective colectomy UC patients (Table 1). Among the emergent colectomy group 88.9% were diagnosed with a VTE postoperatively. Among the 48 UC patients who were diagnosed with VTE, 16.7% were diagnosed after discharge from hospital. No patients died as a complication of the VTE. Postoperative VTE prophylaxis with anticoagulants was prescribed in over 90% of patients. However, VTE prophylaxis was prescribed preoperatively or prior to discharge in less than 20% of patients with UC who underwent emergent colectomy or were emergently admitted to hospital (*i.e.*, medically responsive), respectively (Table 1).

Among all UC patients (n = 1020), UC patients requiring elective colectomy (adjusted OR = 3.69; 95%CI: 1.30-10.44) and emergent colectomy (adjusted OR = 5.28; 95%CI: 1.93-14.45) were significantly more likely to be diagnosed with a VTE as compared to medically responsive UC patients (Table 3). Furthermore, the odds of a VTE significantly increased across time (adjusted OR = 1.10; 95%CI: 1.01-1.20). Patients who underwent emergent colectomy (*i.e.*, elective colectomy excluded) were significantly more likely to develop a VTE (adjusted OR = 4.62; 95%CI: 1.66-12.88) as compared to UC patients who were medically responsive. Furthermore, an in-hospital complication was associated with an increased odds of VTE (adjusted OR = 2.68; 95%CI: 1.42-5.05) (Table 3).

DISCUSSION

This study identified a population-based cohort of over 1000 hospitalised UC patients. All charts were identified to confirm the diagnosis of VTE both in-hospital and following discharge. The study population was stratified according to the indication for admission (*i.e.*, medically responsive UC flare,

Table 1 Characteristics of patients hospitalized for a ulcerative colitis flare, or undergoing a colectomy *n* (%)

Characteristics	Total cohort (*n* = 1020)	Elective colectomy (*n* = 329)	Emergency colectomy (*n* = 309)	Medically responsive (*n* = 382)	*P* value
Thrombosis					< 0.001
No	95.3 (972)	95.1 (313)	91.3 (282)	98.7 (377)	
Yes	4.7 (48)	4.9 (16)	8.7 (27)	1.3 (5)	
Age at Admission (tercile)					0.002
18-32	33.8 (345)	28.6 (94)	31.7 (98)	40.1 (153)	
33-47	32.6 (333)	33.1 (109)	31.1 (96)	33.5 (128)	
48+	33.5 (342)	38.3 (126)	37.2 (115)	26.4 (101)	
Gender					0.022
Male	57.0 (581)	61.4 (202)	58.9 (182)	51.6 (197)	
Female	43.0 (439)	38.6 (127)	41.1 (127)	48.4 (185)	
Smoking					0.011
Current	9.8 (94)	7.9 (25)	7.7 (23)	13.3 (46)	
Ex-smokers	33.0 (317)	30.5 (96)	39.0 (117)	30.1 (104)	
Never	57.2 (549)	61.6 (194)	53.3 (160)	56.5 (195)	
Missing (*n*)	*n* = 60	*n* = 14	*n* = 9	*n* = 37	
Comorbidity					
0 comorbidities	46.3 (472)	48.3 (159)	40.5 (125)	49.2 (188)	0.047
≥ 1 comorbidities	53.7 (548)	51.7 (170)	59.6 (184)	50.8 (194)	
Primary sclerosing cholangitis					0.572
No	97.6 (996)	97.0 (319)	97.7 (302)	98.2 (375)	
Yes	2.4 (24)	3.0 (10)	2.3 (7)	1.8 (7)	
Ankylosing spondylitis or sacroiliitis					0.222
No	99.0 (1010)	99.7 (328)	98.4 (304)	99.0 (378)	
Yes	1.0 (10)	0.3 (1)	1.6 (5)	1.0 (4)	
Episcleritis, uveitis and iritis					0.603
No	98.9 (1009)	98.5 (324)	99.4 (307)	99.0 (378)	
Yes	1.1 (11)	1.5 (5)	0.6 (2)	1.0 (4)	
Disease duration, years					< 0.001
Median (IQR)	3 (0-9)	6 (2-14)	2 (0-7)	1 (0-6)	
Missing (*n*)	*n* = 35	*n* = 18	*n* = 9	*n* = 8	
Cancer/dysplasia					-
No	-	83.0 (273)	-	-	
Yes		17.0 (56)			
Extent of disease					< 0.001
Left-sided	29.4 (265)	23.5 (73)	20.9 (63)	44.5 (129)	
Pancolitis	70.6 (637)	76.5 (237)	79.1 (239)	55.5 (161)	
Missing (*n*)	*n* = 118	*n* = 19	*n* = 7	*n* = 92	
Blood in Stool and Stool Frequency > 5/d[1]					< 0.001
No	27.0 (217)	46.4 (91)	18.9 (54)	22.3 (72)	
Yes	73.0 (588)	53.6 (105)	81.1 (232)	77.7 (251)	
Missing (*n*)	*n* = 215	*n* = 133	*n* = 23	*n* = 59	
5-ASA[2]					< 0.001
No	33.1 (336)	28.0 (91)	26.9 (83)	42.4 (162)	
Yes	66.9 (680)	72.0 (234)	73.1 (226)	57.6 (220)	
Missing (*n*)	*n* = 4	*n* = 4			
Prednisone[2]					< 0.001
No	31.3 (318)	16.6 (54)	22.0 (68)	51.3 (196)	
Yes	68.7 (698)	83.4 (271)	78.0 (241)	48.7 (186)	
Missing (*n*)	*n* = 4	*n* = 4			
Azathioprine/6-mercaptopurine[2]					< 0.001
No	80.7 (820)	69.2 (225)	80.3 (248)	90.8 (347)	
Yes	19.3 (196)	30.8 (100)	19.7 (61)	9.2 (35)	
Missing (*n*)	*n* = 4	*n* = 4			
Infliximab[2]					0.006
No	96.1 (976)	94.8 (308)	94.5 (292)	98.4 (376)	
Yes	3.9 (40)	5.2 (17)	5.5 (17)	1.6 (6)	
Missing (*n*)	*n* = 4	*n* = 4			
Complication in hospital[3]					< 0.001
0 or Clavien I	80.2 (818)	79.9 (263)	64.1 (198)	93.5 (357)	
Clavien II/III/IV	19.8 (202)	20.1 (66)	35.9 (111)	6.5 (25)	
Postoperative heparin					0.641
No	6.9 (44)	6.4 (21)	7.4 (23)	-	
Yes	93.1 (593)	93.6 (307)	92.6 (286)		
Missing (*n*)	*n* = 1	*n* = 1			

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Heparin prophylaxis prior to surgery/discharge[4]				0.310
No	82.9 (572)	-	81.2 (251)	84.3 (321)
Yes	17.1 (118)		18.8 (58)	15.7 (60)
Missing (*n*)	*n* = 1			*n* = 1

[1]Missing data is defined as missing on either the stool frequency, the presence of blood in stool, or both. [2]Defined as medication used prior to or at the time of admission to hospital. No refers to no record of drug use in the medical chart. [3]Complication was classified as Clavien ≥ Ⅱ. [4]Emergent colectomy - heparin prophylaxis in hospital prior to colectomy. Medically Responsive - heparin prophylaxis in hospital prior to discharge.

Table 2 Location of venous thromboembolism *n* (%)

Location of VTE	Total (*n* = 48)	Elective colectomy (*n* = 16)	Emergency colectomy (*n* = 27)	Medically responsive (*n* = 5)
Upper extremity	8 (17.4)	1 (6.3)	6 (22.2)	1 (20.0)
Lower extremity	9 (19.6)	3 (18.8)	6 (22.2)	0
Intra-abdominal	22 (45.8)	11 (68.8)	10 (37.0)	1 (20.0)
Pulmonary embolism	9 (18.8)	1 (6.3)	5 (18.5)	3 (60.0)

VTE: Venous thromboembolism.

Table 3 Independent predictors of venous thromboembolism for all ulcerative colitis patients; those admitted emergently to hospital and were medically responsive or underwent emergent colectomy; and those who underwent an emergent or elective colectomy

	Full cohort VTE (*n* = 1020) Adjusted OR (95%CI)	Emergent and medically responsive cohort VTE (*n* = 690)[1] Adjusted OR (95%CI)	Emergent and elective cohort VTE (*n* = 637)[1] Adjusted OR (95%CI)
Age, yr			
18-32	1.00	1.00	1.00
33-47	1.56 (0.68-3.56)	2.44 (0.81-7.34)	1.35 (0.56-3.27)
≥ 48	1.63 (0.74-3.59)	2.29 (0.79-6.66)	1.65 (0.72-3.75)
Disease course			
Medical responsive	1.00	1.00	Not applicable
Elective colectomy	3.69 (1.30-10.44)	Not applicable	1.00
Emergent colectomy	5.28 (1.93-14.45)	4.62 (1.66-12.88)	1.59 (0.82-3.07)
VTE prophylaxis[2]			
No	Not applicable	1.00	1.00
Yes		2.24 (0.99-5.03)	1.38 (0.32-6.00)
In-hospital complication			
No	1.00	1.00	1.00
Yes	2.68 (1.42-5.05)	2.80 (1.26-6.24)	2.53 (1.32-4.85)
Year	1.10 (1.01-1.20)	Not significant[3]	Not significant[3]

[1]One patient was excluded in each of these cases due to missing data. [2]VTE prophylaxis with anticoagulants (*e.g.*, heparin) was assessed preoperatively/in-hospital for the emergent colectomy and medically responsive cohort, and postoperatively for the emergent and elective colectomy cohort. VTE prophylaxis was not modeled for the entire cohort. [3]*P* value was > 0.1 when fitted into the regression model using stepwise selection. The following variables were tested in the multivariate model, but were not independent predictors in any of the models: sex, disease duration, comorbidities, extra-intestinal manifestations, extent of disease, blood in stool and frequency of bowel movements. 5-ASA: Azathioprine, prednisone, and infliximab; VTE: Venous thromboembolism.

emergent colectomy, or elective colectomy) in order to explore the effect of surgery on the risk of VTE. We demonstrated that colectomy was significantly associated with the development of VTE. VTE occurred in about 1% of the medically responsive UC patients, whereas UC patients who failed to respond to medical management and underwent a colectomy had an over 5-fold increased odds of VTE. Similarly, UC patients undergoing elective colectomy had an over 3-fold increased odds of VTE when compared to medically responsive UC inpatients. In contrast, the risk of VTE was not associated with disease location, or drug utilization including the use of corticosteroids, immunomodulators, and biologics.

VTE occurred in 4.7% of UC patients. These

occurred in a number of locations including extremity, intra-abdominal (*i.e.*, portal and hepatic vein thrombosis), and pulmonary embolism. VTE were confirmed using multiple different testing modalities including chest X-ray, D-Dimer, Doppler ultrasound of the extremities, V/Q scan, CT PE protocol, and angiography. While most VTE were identified following the manifestation of clinical symptoms, most of the intra-abdominal clots were detected incidentally in asymptomatic patients on CT scans performed to assess postoperative symptoms or complications. While incidental cases were primarily identified in postoperative patients following colectomy (11 cases among elective and 10 cases among emergent colectomy), one

incidental intra-abdominal VTE was identified in the medically responsive group. Thus, some cases of VTE that were asymptomatic may have been missed. However, the proportion of clinically relevant VTE that we missed was likely low. For example, a recent study of inpatient and outpatient UC patients who were actively flaring, but were asymptomatic for a DVT, were not found to have any incidentally diagnosed DVT on screening ultrasound[20]. Also, we evaluated every case for readmission to hospital for a VTE within 6 mo of the discharge from hospital admission. Thus, we were able to capture clinically meaningful cases of VTE that were missed in hospital or developed post-discharge. Sixteen percent of UC patients were readmitted to hospital for VTE following discharge from hospital including one patient who was readmitted 6 d after discharge for mesenteric vein thrombosis that led emergent resection of ischemic bowel. Consequently, physicians should be aware of this complication, recognize the signs and symptoms, and have a low threshold to screen for VTE in the extremities and in the abdomen in UC patients.

Current American College of Gastroenterology guidelines recommend VTE prophylaxis for all patients admitted to hospital with an IBD flare as well as all postoperative patients undergoing colectomy[23]. The American College of Chest Physicians (ACCP) guidelines recommend VTE prophylaxis in IBD patients confined to a bed[30]. Though, ambulation alone would not prevent intra-abdominal VTE. In our study, greater than 90% of emergent and elective colectomy patients received VTE prophylaxis postoperatively. Despite the high utilization of postoperative heparin, the occurrence of VTE remained high. Similarly, a smaller study found that despite adequate postoperative heparin use, rates of VTE in post-colectomy patients were over 7-fold higher in UC patients as compared to patients undergoing surgery for colorectal cancer[31]. A randomized controlled trial that included nearly 600 patients with inflammatory bowel disease demonstrated that low dose heparin had significantly lower rates of VTE (2.9%) as compared to patients randomized to enoxaparin (9.0%)[32].

The current ACCP guidelines recommend that patients undergoing abdominal or pelvic surgery for cancer, with a high risk of postoperative VTE (*i.e.*, > 6%) and who do not have increased risk of bleeding, should be considered for both mechanical and pharmacological VTE prophylaxis and extended duration of the latter[30]. Our study was unique from prior work because we explored VTE occurrence up to 6 mo following discharge from hospital. We demonstrated that 16% of our detected VTE were diagnosed after discharge from hospital. Our findings raise the issue of whether the same consideration for extended postoperative VTE prophylaxis should be given for IBD surgeries. Prior studies have reported

lower DVT levels (< 3%) postoperatively for IBD surgeries[31,32], as compared to our study. However, nearly half of our VTE population experienced an intra-abdominal VTE. The clinical significance of intra-abdominal VTE is controversial and depends on the acuity, size, and location of the thrombosis[33,34]. Given the uncertainty, these findings warrant a randomized controlled trial to evaluate the efficacy of VTE prophylaxis for 4 wk postoperatively.

Only 19% of patients admitted with an UC flare who underwent emergent colectomy received preoperative VTE prophylaxis. Similarly, only 16% of patients who were admitted for an UC flare and discharged without colectomy received VTE prophylaxis in-hospital. A recent multicenter chart audit of 29 Canadian hospitals also demonstrated similarly low prophylaxis rates for hospitalized medical patients requiring VTE prophylaxis[35]. Moreover, patients who received VTE prophylaxis were more likely to be diagnosed with a VTE. However, this finding likely reflected disease severity (*i.e.*, confounding by indication) because a meta-analysis indicated that heparin is safe to use in an acute flare of UC[25,36] and randomized controlled trials support the use of VTE prophylaxis in IBD[32]. Thus, in the absence of hemodynamically significant haemorrhage VTE prophylaxis should be prescribed. However, the adequate agent, dose, and duration of VTE prophylaxis in medically managed UC patients need further evaluation.

Our study could not differentiate whether the increased risk of VTE among UC patients undergoing colectomy was due specifically to the colectomy or was caused by disease severity necessitating colectomy. Though, most likely it was due to the combination of disease severity and surgery. Thus, the optimal approach of preventing VTE is to induce and maintain remission in UC. The majority of UC patients were admitted to hospital prior to publications demonstrating efficacy of infliximab in the hospital[37] and outpatient setting[38]. Additionally, recent studies have demonstrated that infliximab significantly reduced the risk of colectomy for up to 3 years following initiation of treatment[39-41]. Because less than 4% of the patients in our study were prescribed infliximab, greater utilization of anti-TNF therapies may lead to reduced colectomy and hence, burden of VTE among UC patients.

Several limitations to this study should be considered. While VTE events that resulted in a readmission to hospital within 6 mo of hospital discharge were captured, UC patients diagnosed and managed for VTE as an outpatient following discharge from hospital would not have been accounted for in this study. Thus, the occurrence of VTE may have been underestimated. While chart review improves the accuracy of the data and minimizes misclassification bias that occur with studies using administrative databases[29,42], some

data were missed due to incomplete recording in the medical chart. For example, we were not able to account for the use of oral contraceptive pills prior to hospitalization due to unreliable recording of this data. This study was not able to confirm if other forms of VTE prophylaxis such as graduated compression stockings or intermittent pneumatic compression devices for hospitalized UC patients were utilised. However, these modalities are only recommended if heparin is contraindicated because they are less effective at preventing proximal extremity and intra-abdominal VTE. Also, due to the retrospective nature of chart reviews we were not able to assess the number of flares from diagnosis to admission to hospital or to define disease severity using a validated disease activity index (*e.g.*, Mayo score). Finally, despite the advantages of designing a population-based study, regional practice pattern differences may limit generalizability. Consequently, we recommend hospitals assess their own utilization of heparin prophylaxis and correlate these with VTE outcomes.

VTE occurred commonly in UC patients who underwent emergent (8.7%) and elective (4.9%) colectomy despite greater than 90% rate of postoperative heparin prophylaxis. In contrast, about 1% of medically responsive UC inpatients experienced a VTE, despite a 16% prophylaxis rate. Thus, VTE prophylaxis should be prescribed at time of admission in all IBD patients, and VTE prophylaxis for flaring UC patients should be considered a quality indicator of best clinical practice. This population-based study confirmed that the necessity of colectomy was significantly associated with VTE. The high rates of VTE in UC patients who underwent colectomy despite postoperative VTE prophylaxis highlights potentially serious outcomes associated with surgical management of UC. Consequently, these findings emphasize the importance of optimizing medical therapy for UC patients.

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COMMENTS

Background
Ulcerative colitis (UC) is a chronic inflammatory condition of the large colon that affects young individuals in the prime of their lives. Most patients with UC require daily medications to control inflammation. When these medications do not work UC patients require an operation (*i.e.*, colectomy) to remove their large bowel.

Research frontiers
Patients with UC are at increased risk of developing a venous thromboembolism

(VTE), which is a potentially life-threatening complication. Potential risk factors for developing VTE among patients with UC include acute flares, hospitalization, advanced age, comorbidities, colectomy, and malnutrition. Understanding the leading risk factors of VTE for patients with UC will allow physicians to optimize prevention of VTE.

Innovations and breakthroughs
The overall occurrence of VTE among hospitalized patients with UC was nearly 5%. However, the risk of VTE was low (about 1%) among flaring UC patients who were responsive to medical in-hospital management. In contrast, patients with UC who underwent an elective colectomy (5%) or emergent colectomy (8.7%) had significantly higher occurrence of VTE. In contrast, about 1% of medically responsive UC inpatients experienced a VTE.

Applications
Prescription of VTE prophylaxis for UC patients hospitalized for flare was suboptimal (< 20%). In contrast, VTE prescriptions postoperatively were high (> 90%) following a colectomy for UC. Thus, this data supports both VTE prophylaxis and aggressive medical management of ulcerative colitis patients to prevent VTE formation.

Terminology
Venous thromboembolism is a blood clot that forms within the venous circulation. International Classification of Diseases is a set of codes used by hospital health records to document diseases. These coded data can be used for research and surveillance purposes.

Peer review
"This is an excellent original contribution analyzing cohort of 1020 hospitalised UC patients towards risk of VTE. The Authors determined that patients who underwent elective or emergent colectomy had 4-5-fold increased risk of VTE when compared to UC patients treated non-surgically."

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