Portomesenteric Venous Thrombosis in Patients Undergoing Surgery for Medically Refractory Ulcerative Colitis

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Background: Portomesenteric venous thrombosis (PMVT) is an under-recognized complication of colorectal surgery. The aim of this study was to describe the rate and risk factors for PMVT in patients undergoing surgery for medically refractory ulcerative colitis (UC).

Methods: A retrospective review of medically refractory UC patients who underwent surgery between January 2010 and December 2016 at a single tertiary care center was conducted. PMVT was defined as thrombus within the portal, splenic, superior, or inferior mesenteric vein on postoperative abdominal computed tomography scans. Factors associated with PMVT on univariable analysis were tested in multivariable analysis. Clinical relevance of risk factors was examined with receiver operating characteristic curves and Kaplan-Meier curves.

Results: A total of 434 patients were identified. Postoperative venous thromboembolism (VTE) prophylaxis was administered to 428 (98.5%) inpatients for a mean duration of 7.7 ± 0.17 days. PMVT developed in 36 (8.3%) patients a mean interval of 55.3 ± 10.8 days after index surgery. The majority of PMVT occurred after subtotal colectomy, and the most common initial symptom was abdominal pain. Preoperative C-reactive protein (CRP) was associated with PMVT (odds ratio, 1.01; 95% confidence interval, 1.00–1.02; $P = 0.01$), and the optimal predictive CRP threshold was 45 mg/L. The rate of PMVT development was greater for patients with CRP >45 mg/L ($P = 0.01$).

Conclusions: PMVT can present as abdominal pain and occur multiple weeks after discharge. Further studies are needed to identify the appropriate postoperative outpatient thrombosis prophylaxis regimen for at-risk patients.

Key Words: mesenteric venous thrombosis, ulcerative colitis, surgery

INTRODUCTION

Portomesenteric venous thrombosis (PMVT) is an under-recognized complication of colorectal surgery, with reported postoperative incidence rates of 3%–10%.[1–6] The clinical manifestations of PMVT are variable and range from nonspecific abdominal pain to life-threatening bowel ischemia.[7] PMVT is most commonly diagnosed via computed tomography (CT) of the abdomen with intravenous contrast.[8] Immediate initiation of systemic anticoagulation is the mainstay of treatment and is associated with venous recanalization, prevention of thrombus recurrence, and decreased mortality in the case of recurrence.[5, 9] The duration of anticoagulation is 6 months for patients with known reversible conditions and lifelong for patients with prothrombotic states.[10, 11]

Risk factors associated with the development of PMVT have been widely categorized as systemic or locoregional. Systemic factors include inherited prothrombotic states such as antithrombin deficiency, protein C and S deficiency, factor V Leiden mutation, and prothrombin mutation and acquired prothrombotic states such as sepsis, malignancy, and cirrhosis. Locoregional factors relate to alterations in portovenous blood flow from surgical manipulation of mesenteric vessels and ligation of the splenic vein.[12, 13] PMVT has been reported to occur in inflammatory bowel disease patients regardless of their disease activity, reflecting the inherent increased risk of venous thromboembolism in these patients.[11]

Received for publications March 26, 2019; Editorial Decision May 23, 2019.

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Supported by: The authors declare no funding support.

Conflicts of interest: The authors have no relevant conflicts of interest or disclosures.

Author contributions: M.K.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis; M.R.: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content; M.P.: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content; A.R.: analysis and interpretation of data, statistical analysis, critical revision of the manuscript for important intellectual content; A.G.: study concept and design, critical revision of the manuscript for important intellectual content; S.K.: study concept and design, critical revision of the manuscript for important intellectual content; P.S.: study concept and design, critical revision of the manuscript for important intellectual content; M.D.: study concept and design, critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript. Guarantor of the article: Marla C. Dubinsky is the submission's guarantor and takes responsibility for the integrity of the work as a whole, from inception to published article.

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doi: 10.1093/ibd/izz169
Published online 2 August 2019

Only 3 studies to date have examined the risk factors for PMVT in patients undergoing colorectal surgery. These studies included patients who underwent colorectal surgery for a wide range of indications such as colon cancer, rectal cancer, diverticulitis, ulcerative colitis (UC), Crohn's disease (CD), and polyposis. Reported preoperative risk factors include younger age, obesity, hypoalbuminemia, and steroid use, and operative risk factors include restorative proctocolectomy.[2–4]

There are few data on the true incidence and risk factors of symptomatic PMVT in patients undergoing surgery for medically refractory UC. To that end, the aim of this study was to describe the rate and associated risk factors of PMVT development in patients undergoing surgery for medically refractory UC. We sought to identify high-risk patients who would benefit from extended postoperative venous thromboembolism (VTE) prophylaxis.

METHODS

Study Population

This was a retrospective review conducted at a single tertiary care high-volume IBD center. Institutional review board approval was obtained. All patients who underwent surgery for medically refractory UC between January 2010 and December 2016 were identified through hospital electronic medical records. Patients with CD, inflammatory bowel disease unclassified (IBDU), or disease complicated by dysplasia or malignancy were excluded.

Data Collection

In-depth chart review was performed for all patients, and data were collected. Collected patient demographics and disease characteristics included body mass index (BMI), sex, age at surgery, smoking status at surgery (active or inactive), UC disease duration (months), UC disease extent according to the Montreal classification (ulcerative proctitis, left-sided UC, extensive UC), personal history of thromboembolic disease such as deep venous thrombosis (DVT) or pulmonary embolism, and previous diagnosis of prothrombotic disease such as antithrombin deficiency, protein C and S deficiency, factor V Leiden mutation, and prothrombin mutation. Preoperative labs such as hemoglobin, platelets, C-reactive protein (CRP), and albumin drawn within the 2 weeks preceding surgery were recorded. Use of steroids and/or biologics (adalimumab, infliximab, golimumab, certolizumab, vedolizumab) within the 3 months preceding surgery was recorded. Use of oral contraceptives and/or immunomodulators (methotrexate, azathioprine, mercaptopurine, cyclosporine, tacrolimus) within the month preceding surgery was recorded. Operative characteristics such as acuity (urgent or elective), operative procedure (1-, 2-, or 3-stage restorative proctocolectomy), administration and type of preoperative VTE prophylaxis (inpatient regimen and surgical induction dose) and postoperative VTE prophylaxis (inpatient and outpatient regimen), cumulative operative time (minutes), intraoperative blood transfusions, emergent reoperation during the same admission, and total hospital length of stay (days) were recorded. Pre- and postoperative abdominal CT scans within 6 months of each surgical stage were reviewed, and indications and findings were collected.

Outcome Measures

Urgent surgery was defined as that performed on an inpatient who had failed maximum medical therapy. One-stage restorative proctocolectomy (RPC) surgery was defined as total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) construction. Two-stage RPC surgery was defined as (1) TPC with immediate IPAA construction and diverting ostomy with (2) subsequent ostomy closure. Three-stage RPC surgery was defined as (1) subtotal colectomy (STC) followed by (2) completion of proctectomy with IPAA construction and diverting ostomy and (3) subsequent ostomy closure.

PMVT was defined as any thrombus/thrombi within the portal, splenic, superior, or inferior mesenteric vein noted on abdominal CT scans performed within 6 months of each surgical stage. Follow-up abdominal imaging to determine clot resolution was reviewed in patients with reported PMVT when available.

Statistical Analysis

Quantitative data were expressed as the mean ± standard error of the mean (SEM) and were statistically compared with *t* tests. Qualitative data were compared with either the chi-square test or Fisher exact test when feasible. Multiple logistic regression using the forward conditional method was performed to identify the factors that were independently associated with mesenteric thrombosis during the study period.

Receiver operating characteristic (ROC) curves were constructed for the relevant laboratory tests that were predictive of PMVT. The area under the curve was determined and statistically compared with the reference line.[14] The optimal threshold that maximized the Youden index (specificity + sensitivity – 1) was determined.[15] The subjects were then dichotomized based on the optimal threshold. Time-to-event curves for the 2 subgroups were plotted using the Kaplan-Meier method. The curves were statistically compared using the log-rank test. Statistical calculations were performed using SPSS for Windows (version 24; IBM, Armonk, NY, USA). A P value of <0.05 was considered statistically significant. ROC and Kaplan-Meier curves were constructed using SigmaPlot (version 13.0; Systat Software, San Jose, CA, USA).

RESULTS

Study Population

A total of 514 patients were identified from electronic medical records, of which 80 patients were excluded due to a diagnosis of dysplasia, CD, or IBDU. The remaining 434 patients underwent surgery for medically refractory UC between January 2010

and December 2016. Patient demographics and baseline disease and surgical characteristics are noted in Tables 1 and 2. History of thromboembolic disease was noted in 18/434 (4.1%) patients; however, no patient had a previous diagnosis of prothrombotic disease. Preoperative lab data were available for 220 patients, and the mean preoperative CRP was 53.9 ± 4.3 mg/L.

TABLE 1. Patient Demographics and Disease Characteristics

	All Patients (n = 434)	Thrombosis (n = 36)	No Thrombosis (n = 398)	*P*
BMI, kg/m^2	22.9 ± 0.3	23.1 ± 1.0	22.9 ± 0.3	0.85
Sex				0.17
Female	203 (46.8)	21 (58.3)	182 (45.7)	
Male	231 (53.2)	15 (41.7)	216 (54.3)	
Age at surgery, y	35.4 ± 3.3	39.5 ± 2.8	35.1 ± 3.6	0.71
Active smoking at surgery	16 (3.7)	2 (5.6)	14 (3.5)	0.63
Disease duration, mo	88.9 ± 4.9	97.5 ± 16.7	88.1 ± 5.2	0.60
Disease extent				0.22
Left-sided	52 (12.0)	2 (5.6)	50 (96.2)	
Extensive	382 (88.0)	34 (94.4)	348 (87.4)	
Previous thromboembolic disease	18 (4.1)	3 (8.3)	15 (3.8)	0.16
Preoperative values				
CRP, mg/L	53.8 ± 4.3	87.9 ± 18.9	50.5 ± 4.3	0.01
Albumin, g/dL	3.0 ± 0.04	2.9 ± 0.1	3.0 ± 0.04	0.53
Hemoglobin, g/dL	10.4 ± 0.1	10.6 ± 0.3	10.3 ± 0.1	0.47
Platelet count, ×10^3/uL	350.0 ± 7.2	345.5 ± 21.2	350.4 ± 7.6	0.85
Preoperative medications[a]				
Oral contraceptives	32 (7.4)	3 (8.3)	29 (7.3)	0.74
Steroids	313 (72.1)	26 (72.2)	287 (72.1)	0.57
Biologics	281 (64.7)	28 (77.8)	253 (63.6)	0.20
Immunomodulators	157 (36.2)	11 (30.6)	146 (36.7)	0.47
Preoperative VTE prophylaxis	138 (31.8)	12 (33.3)	126 (31.7)	0.85

Data are presented as mean ± standard error or No. (%).
[a]Multiple medications for certain patients.

TABLE 2. Operative Characteristics

	All Patients (n = 434)	Thrombosis (n = 36)	No Thrombosis (n = 398)	*P*
Acuity of surgery				0.15
Urgent	166 (38.2)	18 (50)	148 (37.2)	
Elective	268 (61.8)	18 (50)	250 (62.8)	
Type of surgery				0.88
1-stage RPC	14 (3.2)	1 (2.8)	13 (3.3)	
2-stage RPC	107 (24.7)	12 (33.3)	95 (23.9)	
3-stage RPC	229 (52.8)	17 (47.2)	212 (53.3)	
STC with EI	48 (11.1)	4 (11.1)	44 (11.1)	
TPC with EI	36 (8.3)	2 (5.6)	34 (8.5)	
Intraoperative blood transfusion	27 (6.2)	1 (2.8)	26 (6.5)	0.72
Total operative time, min	386.2 ± 6.9	382.6 ± 21.2	386.5 ± 7.4	0.88
Postoperative VTE prophylaxis	428 (98.6)	36 (100)	392 (98.5)	0.99
Emergent reoperation	48 (11.1)	6 (16.7)	42 (10.6)	0.03
Total length of hospital stay, d	18.1 ± 0.4	20.5 ± 2.0	17.8 ± 0.4	0.10

Data are presented as mean ± standard error or No. (%). RPC, restorative proctocolectomy; STC, subtotal colectomy; TPC, total proctocolectomy; EI, end ileostomy; VTE, venous thromboembolism.

Urgent surgery was performed in 166/434 (38.2%) patients and elective surgery in 268/434 (61.7%). Preoperative VTE prophylaxis was administered to 138/166 (83.1%) patients who underwent urgent surgery and was not administered to any patient who underwent elective surgery. The mean length of hospital stay for all patients was 18.1 ± 0.4 days and was significantly greater in patients who underwent urgent surgery (21.6 ± 0.7 days) as compared with those who underwent elective surgery (15.9 ± 0.5 days; $P < 0.001$).

Three-stage RPC was performed in 229/434 (52.8%) patients, 2-stage RPC in 107/434 (24.7%), STC with end ileostomy in 48/434 (11.1%), TPC with end ileostomy in 36/434 (8.3%), and 1-stage RPC in 14/434 (3.2%) (Table 2). Postoperative VTE prophylaxis was administered to 428/434 (98.5%) inpatients, and the most common regimen was subcutaneous heparin every 12 hours. The mean duration of inpatient postoperative VTE prophylaxis was 7.7 ± 0.17 days. No patients were discharged with postoperative VTE prophylaxis.

PMVT

Of 434 patients, 91 (21.0%) had preoperative imaging without evidence of PMVT and 205 (47.2%) had postoperative diagnostic abdominal CT scans. There was no significant difference in demographics or disease characteristics among patients who underwent postoperative imaging and those who did not; however, the former had significantly longer cumulative operative times (409.1 ± 9.0 minutes vs 357.5 ± 10.6 minutes; $P < 0.001$), longer hospital length of stay (11.0 ± 0.5 days vs 8.3 ± 0.4 days; $P < 0.001$), and a higher rate of emergent reoperation (19.8% vs 1.6%; $P < 0.001$). The most common indications for postoperative CT scans were acute abdominal pain, fever, and leukocytosis. Acute PMVT was identified in 36/434 (8.3%) patients a mean interval of 55.3 ± 10.8 days after the index surgery. Among these, 29/36 (80.6%) had staged procedures and 8/36 (22.2%) patients had initial postoperative imaging that did not reveal thrombus. PMVT developed after the first stage (TPC and IPAA for 2-stage procedures, STC and end ileostomy [EI] for 3-stage procedures) in 16 patients and after the final stage (ostomy closure) in 5 patients (Table 3).

The most common locations for PMVT were the superior mesenteric vein and the right branch of the portal vein (Table 4). Thrombus in the main portal vein occurred in only 5 patients. Approximately two-thirds of the reported PMVTs were occlusive. There was no radiographic evidence of chronicity such as collateralization noted on any abdominal CT scan.

All 36 patients diagnosed with PMVT received therapeutic anticoagulation with enoxaparin, warfarin, or rivaroxaban for 6 months after diagnosis. Abdominal CT scans within 6 months of anticoagulation completion were available for 26/36 (72.2%) patients, all of which noted PMVT resolution. No patients diagnosed with PMVT developed bowel infarction or required surgical intervention.

The demographics and disease and surgical characteristics of patients with and without PMVT are shown in Tables 1 and 2. In univariable analysis, subjects with PMVT had significantly higher preoperative CRP values and a greater rate of emergent reoperation within the same admission. In multivariable analysis, preoperative CRP remained associated with an increased risk of PMVT (odds ratio, 1.01; 95% confidence interval, 1.01–1.02; $P = 0.01$).

An ROC curve was constructed for preoperative CRP as a predictor of PMVT (Fig. 1). The area under the ROC curve was 0.65 ± 0.08 ($P = 0.03$ compared with the reference line). The optimal threshold for serum CRP as a predictor of PMVT was 45 mg/L, as determined by the Youden index. Using this threshold, subjects were divided into a low-CRP group and a high-CRP group. The time to PMVT development was plotted using the Kaplan-Meier method for the 2 subgroups (Fig. 2). The rate of developing PMVT was significantly greater for the high-CRP group ($P = 0.01$).

TABLE 3. Timing of Postoperative Thrombosis Occurrence

n = 36	
STC with EI	4 (11.1)
TPC with EI	2 (5.6)
1-stage RPC	1 (2.8)
2-stage RPC	12
• After TPC and IPAA	8 (22.2)
• After ostomy closure	4 (11.1)
3-stage RPC	17
• After STC and EI	8 (22.2)
• After completion of proctectomy and IPAA	8 (22.2)
• After ostomy closure	1 (2.8)

Data are presented as No. (%). STC, subtotal colectomy; EI, end ileostomy; TPC, total proctocolectomy; RPC, restorative proctocolectomy; IPAA, ileal pouch anal anastomosis.

TABLE 4. PMVT Characteristics

n = 36	
Location[a]	
Main portal vein	5 (13.9)
Right portal vein branch	12 (33.3)
Left portal vein branch	3 (8.3)
Single portal vein peripheral branch	7 (19.4)
Multiple portal vein peripheral branches	4 (11.1)
Superior mesenteric vein	13 (36.1)
Occlusive	24 (66.7)
Nonocclusive	12 (33.3)

Data are presented as No. (%).
[a]Multiple locations for certain patients.

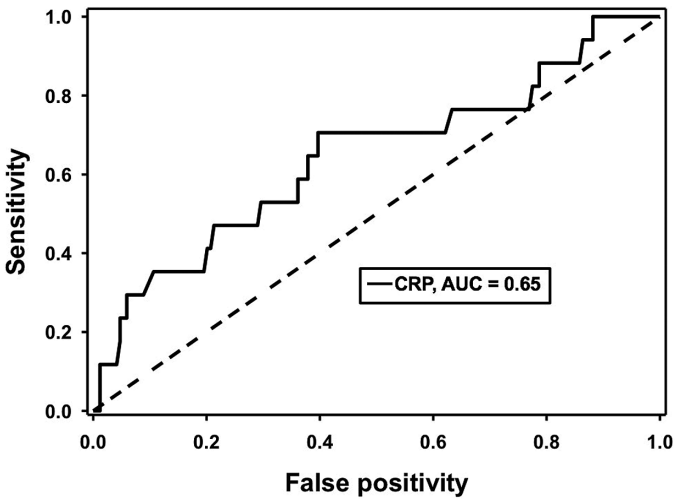

FIGURE 1. Predictive value of CRP for PMVT. ROC curve for preoperative CRP as a predictor of thrombosis, AUC 0.65 ± 0.08 ($p = 0.03$ compared with the reference line). The optimal threshold for serum CRP as a predictor of PMVT was 45 mg/L, as determined by the Youden index.

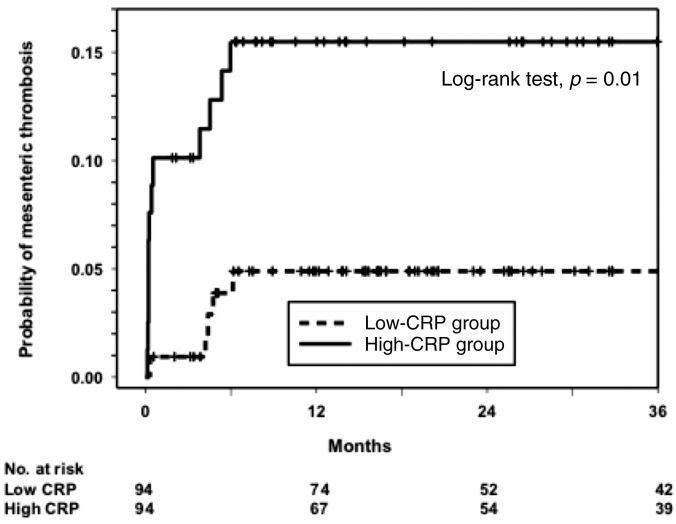

FIGURE 2. Kaplan-Meier estimates of PMVT development. The Youden index was used to identify a CRP value of 45 mg/L as the optimal threshold. A low CRP was defined as ≤45 mg/L; high CRP was defined as >45 mg/L.

DISCUSSION

The rate of postoperative PMVT in our study was approximately 8%, comparable to previously reported incidence rates of 3%–10%.[1–6] The mean duration of postoperative VTE prophylaxis was 7.7 ± 0.17 days, and the mean time to thrombosis was 55.3 ± 10.8 days after the index surgery. Preoperative CRP levels >45 mg/L were a significant risk factor for PMVT on univariable, multivariable, and ROC analysis.

Patients with IBD have a 2–4 times increased risk of VTE after colorectal surgery, regardless of the type or indication of surgery.[16–19] Recent data have suggested that this increased risk persists for 6 weeks after discharge from an admission that included major surgery and standard-of-care VTE prophylaxis.[20, 21] In our study, PMVT occurred 7–8 weeks after index surgery in patients who received postoperative VTE chemoprophylaxis for 1 week. We are limited in our ability to precisely identify the timing of PMVT development because not all of our patients had postoperative imaging at specific time points. Nonetheless, 20% of patients who developed PMVT in our cohort had initial postoperative imaging with normal vasculature despite subsequent imaging with PMVT. These results suggest that IBD patients remain hypercoagulable beyond the perioperative period. We were unable to assess the impact of VTE prophylaxis on the development of PMVT in our patients because all received inpatient postoperative VTE prophylaxis; however, none received outpatient postoperative VTE prophylaxis.

The association between preoperative CRP levels and PMVT development has not been previously reported to the best of our knowledge. Increased CRP values are reflective of active inflammation and have been reported to be independently associated with VTE development in non-IBD patients.[22] The relationship between inflammation and hypercoagulability in IBD patients has been well established since 2010, when Grainge et al. reported a 8.4-fold increased risk of developing venous thromboembolism during acute flares of IBD.[23] Our results suggest that this association may extend to the postoperative period and that patients with preoperative CRP values >45 mg/L are most at risk for PMVT development despite undergoing a curative colectomy and presumed resolution of inflammation. Previous studies have reported a persistent risk of VTE after colectomy for medically refractory disease in UC patients, with an increase in cumulative incidence of VTE from 1.3% at 7 days after surgery to 4.3% at 90 days after surgery.[24] There may be undetermined hypercoagulable factors associated with inflammation that persist despite curative colectomy and prolong the postoperative risk of thrombosis.

Interestingly, the use of preoperative steroids had no impact on the development of PMVT in our study. Previous studies have reported conflicting results regarding the risk of preoperative steroid use on thrombosis development. In a study published by Gu et al., preoperative steroid use was significantly associated with PMVT development in UC patients undergoing RPC on both univariable and multivariable analysis.[4] Although there is no risk of hypercoagulability with steroids per se, their use is a surrogate of severe disease activity and inflammation, which is independently associated with thrombosis risk. In a subsequent study published by Gorgun et al., preoperative steroid use was not associated with thrombosis development, though patients with a variety of indications for colectomy were included.[3]

Our study had a number of limitations. First, it was a retrospective review subject to biases in selection and outcome assessment. Only half of our patients had available preoperative lab data, and pre- and postoperative imaging was not routinely

performed for all patients. Computed tomography scans were only performed for symptomatic patients at the discretion of their physician, and therefore asymptomatic PMVTs may have been missed. Patients who underwent CT scans had longer cumulative operative times and hospital lengths of stay and a higher rate of emergent reoperation compared with patients who did not undergo imaging. These patients were likely more ill and may have been predisposed to the development of PMVT; however, these factors were not significant on univariable or multivariable analysis of the larger cohort. Second, outcomes data and complications related to the development of PMVT were not collected. Patients who developed PMVT had longer cumulative hospital stays compared with those who did not, though this did not reach significance in our cohort. Previous studies have reported that PMVT development resulted in an increased readmission rate and subsequent rates of pouchitis; however, due to the lack of long-term follow-up data, we were unable to report such findings or significantly comment on the morbidity associated with the diagnosis.[4, 6] Third, PMVT was defined uniformly as any thrombus/thrombi within the portomesenteric vasculature, although its CT presentation can vary from single nonocclusive thrombus in a main vessel to multiple occlusive thrombi in peripheral branches. Similar to previous studies, our small sample size and limited number of events make it difficult to compare different PMVT presentations.

CONCLUSIONS

PMVT can present as abdominal pain and occur multiple weeks after discharge. Recent literature has recommended prolonged postdischarge VTE prophylaxis in certain high-risk IBD patients; however, no standardized guidelines for patient selection or prophylaxis regimens exist.[25, 26] This study is important as it assists with the identification and risk stratification of UC patients who would benefit from extended postoperative thrombosis prophylaxis. Additional studies are needed to validate our findings and identify other risk factors.

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