Clinical Epidemiology

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ORIGINAL RESEARCH

Venous Thromboembolism After Total Colectomy in Inflammatory Bowel Disease: Risk Factors and Mortality - a Danish Population-Based Cohort Study

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Purpose: Total colectomy is a key intervention in inflammatory bowel disease (IBD) management and a high-risk procedure for postoperative venous thromboembolism (VTE). We investigated risk factors for postoperative VTE and VTE-associated mortality in patients with IBD undergoing total colectomy.

Patients and Methods: We conducted a population-based cohort study using Danish registries (1996–2021), including all patients with IBD who underwent total colectomy (n=5303). We calculated the 90-day cumulative risk of VTE and used Cox regression to assess the association between potential risk factors and VTE. We used the Kaplan–Meier method to calculate 1-year mortality after VTE, and we compared mortality between patients with and without VTE using Cox regression as an estimate of the mortality rate ratio.

Results: The 30-day VTE risk was 0.6% in patients with Crohn's disease and 1.3% in those with ulcerative colitis. During this period, the strongest risk factors were age (adjusted hazard ratio 3.95 [95% CI 1.87–8.37]) for 41–60 years and 2.96 [1.30–6.75] for ≥60 years vs ≤40 years), calendar year of total colectomy (3.84 [1.10–13.34] for 2014–2020 vs 1996–2001), high comorbidity burden (2.14 [0.94–4.88] vs low comorbidity), IBD duration <1 year (1.84 [0.81–4.16] vs 1–5 years), male sex (1.56 ([0.92–2.64]), and corticosteroid use (1.55 [0.86–2.79]). In secondary analyses, comparing preoperative systemic corticosteroid use to non-use, we found a twofold higher 30-day VTE rate. Most associations persisted for 31–90 days, though with some attenuation. The 1-year mortality risk after VTE was 21.0% (hazard ratio of 7.65 [95% CI, 3.12–18.73]).

Conclusion: Several patient and clinical factors were associated with elevated postoperative VTE risk, and VTE after total colectomy carried a substantially increased 1-year mortality. These findings may help identify high-risk subgroups and inform future studies of extended thromboprophylaxis and perioperative management in IBD.

Keywords: inflammatory bowel disease, venous thromboembolism, mortality, colectomy, cohort study

Introduction

Patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), often require surgical management of their disease during their lifetime.[1] IBD-related surgery is associated with a high risk of complications,[2] including an up to 9% 30-day mortality after emergency surgeries.[3,4] A common and potentially fatal complication in IBD patients undergoing surgery is venous thromboembolism (VTE).[5]

The pathways linking VTE to IBD and surgery are multifactorial and not fully understood.[6] Nonetheless, the VTE risk after IBD-related colorectal surgery has been reported to be 2–3% within 30 days.[7–11] Studies have shown that postoperative VTE risk is higher in patients with IBD than in patients without IBD undergoing similar surgical procedures, with UC patients at greater risk than those with CD.[7,10,12] Procedure characteristics also influence risk,

https://doi.org/10.2147/CLEP.S590446
Received: 30 December 2025
Accepted: 24 April 2026
Published: 1 May 2026

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with major colorectal resections, particularly total colectomy and proctocolectomy, as those with the highest postoperative VTE risk.[11] In addition, surgical indications such as abdominal and pelvic cancer, active cancer treatment, high age, obesity, and poor preoperative physical condition are factors known to be associated with a particularly high VTE risk.[13–15] Systemic corticosteroids may further promote thrombosis and are often prescribed during IBD flares, usually when patients are hospitalized and may require IBD-related surgery.[16–18] Despite these recognized risk factors, no clear guidelines exist for extended thromboprophylaxis after IBD-related surgery, partly due to limited evidence and ongoing uncertainty about which patients are at sufficiently high risk to warrant extended treatment.[19,20]

Although total colectomy for IBD is recognized as a high-risk procedure, no study has assessed postoperative VTE risk according to patient and clinical characteristics. Furthermore, evidence on mortality after a VTE in patients undergoing IBD-related surgery remains uncertain.[9] We therefore conducted a nationwide cohort study with two aims. First, we examined patient and clinical characteristics as potential risk factors for VTE after IBD-related total colectomy. In secondary analyses, we examined the association between preoperative systemic corticosteroid use and postoperative VTE after total colectomy. Second, we evaluated one-year mortality following postoperative VTE.

Materials and Methods

Setting

We conducted this population-based cohort study using administrative and health registry data covering the entire Danish population during the period from January 1, 1996, to December 31, 2021. We obtained data from the Danish Civil Registration System,[21] the Danish National Patient Registry,[22] the National Prescription Registry,[23] and the Danish Register of Causes of Death.[24] Information on these data sources is provided in Supplementary Box 1.

In Denmark, all residents have universal access to tax-funded healthcare.[25] The Danish Civil Registration System assigns a unique registration number to each resident at birth or upon immigration.[21] The registration number allows accurate individual-level linkage of data between the Danish health registries. This study was registered with the Danish Data Protection Agency on behalf of Aarhus University (record number 2016-051-000001/2624).

Patients with Inflammatory Bowel Disease and Total Colectomy

Using the Danish National Patient Registry, we identified all patients with IBD who underwent total colectomy in Denmark from January 1, 1996, to September 30, 2021. (See Supplementary Table 1 for procedure and diagnosis codes). We used both primary (main reason for hospitalization) and secondary (diagnoses supplementing the primary diagnosis) hospital records of an IBD diagnosis. We defined IBD as two or more records with an IBD diagnosis code any time before or up to 60 days after total colectomy, including diagnoses recorded before 1996. The 60-day postoperative window was included to allow for cases diagnosed incidentally after histological examination. This definition has previously been validated against medical record review and shown a high positive predictive value of 95% for identifying true IBD cases in the Danish National Patient Registry.[26] We categorized patients by IBD type according to the diagnosis closest to the total colectomy date. In cases of discrepancies between pre- and postoperative IBD diagnoses, we used the postoperative diagnosis, assuming that this diagnosis reflected histological confirmation (n=164). Patients recorded with both UC and CD on the day used to define their IBD type were considered in the CD group, since Crohn's colitis may initially be misdiagnosed as UC (due to Crohn's colitis, for example), whereas the reverse is less likely.[27] We included patients with a procedure code for total colectomy through September 30, 2021, to ensure at least 90 days of follow-up.

Venous Thromboembolism

The primary outcome was an inpatient or outpatient clinic discharge diagnosis (primary or secondary) of VTE, including DVT and PE, as recorded in the Danish National Patient Registry and the Danish Register of Causes of Death after the date of total colectomy surgery. Previous validation studies have shown that DVT and PE coding in the Danish National Patient Registry have a positive predictive value of 86–90%.[28] We included additional codes for splanchnic vein thrombosis, as it is associated with IBD and surgery. (See Supplementary Table 1 for VTE codes).[29,30] We did not

include VTE diagnoses recorded solely in emergency departments due to the low positive predictive value of the coding, as VTE often is a working diagnosis in that setting.[28,31] Patients referred from the emergency department to specialized hospital wards are registered as inpatient admissions in the Danish National Patient Registry, so only a small proportion of patients are recorded solely as emergency department contacts.[32]

Potential Risk Factors for Venous Thromboembolism

We obtained information on the following potential risk factors that may influence VTE risk: sex, age at total colectomy (0–40, 41–60, and 60+ years), calendar period of total colectomy (1996–2001, 2002–2007, 2008–2013, and 2014–2021), subtype of IBD, admission type (elective/emergency), surgical approach (open/laparoscopic), type of colectomy (restorative proctocolectomy ± ileostomy, proctocolectomy with ileostomy, colectomy with ileostomy, colectomy with ileorectal anastomosis, proctocolectomy with Koch reservoir, and other form of colectomy), preoperative length of hospital stay (0–3, 4–7, and 7+ days), indication for colectomy (colorectal cancer/medically refractory IBD), and IBD duration before total colectomy (<1, 1–5, and 5+ years). (See Supplementary Table 1 for codes and definitions). Furthermore, we included information on medical treatment for IBD within 90 days before or on the date of total colectomy from both the National Prescription Registry and the Danish National Patient Registry. IBD patients were subsequently categorized into six treatment groups: no treatment, any treatment, corticosteroids (both topical and systemic), immunosuppressants, biologics, and combination therapy (see Supplementary Table 2 for codes and definitions). Combination therapy was defined as the use of both biologic and immunosuppressive medications within the 90-day window. Moreover, to measure the burden of comorbidity, we identified diagnoses included in the Charlson Comorbidity Index (CCI) from the Danish National Patient Registry, recorded before or on the date of total colectomy. (See Supplementary Table 3 for codes).[33,34] We used a modified CCI that excluded colorectal cancer and additionally included atrial fibrillation/flutter and obesity, because these conditions are associated with VTE. We then calculated CCI scores to assign patients to one of three comorbidity subgroups: low (CCI score of 0); medium (CCI score of 1–2); and high (CCI score of 3 or more).

Statistical Analysis

We characterized patients using summary statistics, and we followed patients from the date of total colectomy until the occurrence of a first-time VTE diagnosis, death, emigration, or the end of the study on December 31, 2021, whichever came first. Because recent guidelines advise high-risk patients to receive extended thromboprophylaxis with low-molecular-weight-heparin (LMWH) for four weeks post-surgery,[19] and because major surgery is considered a transient provoking risk factor for VTE within the first 12 weeks post-surgery,[15] we divided follow-up into two periods: 0–30 and 31–90 days. Due to the limited number of events, our analysis focused only on overall VTE and overall IBD; stratified analyses by VTE subtype and IBD subtype are not reported.

We calculated the 30-day and 90-day absolute VTE risk using the cumulative incidence function, treating death as a competing risk. Cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazards regression models that included all variables specified above, yielding mutually adjusted estimates. There were no missing data for the analysis. The proportional hazard assumption was evaluated using Schoenfeld residuals and was met for the models.

Mortality After Venous Thromboembolism

We identified patients with a first-time VTE within 90 days after total colectomy and defined the VTE date as "index date". For each VTE patient, we matched up to 10 comparators by sex, age at colectomy (±1 year), and calendar year of colectomy, with replacement.[35] Comparators had to be alive, living in Denmark, and free of VTE at the same post-operative time point as the matched VTE patient. They were then assigned an index date equal to their own colectomy date plus the matched patient's time from colectomy to VTE. This matched design ensured that follow-up for mortality began at the same time since surgery in both groups, thereby avoiding the immortal time bias that would arise if VTE was treated as a baseline characteristic from the date of colectomy in the full cohort. If a comparator developed VTE during follow-up, the comparator entered the VTE cohort but also remained in the comparison cohort.[35] Follow-up for mortality began on the index date and ended at death, emigration, or the end of study, December 31, 2021. We estimated 30-, 90-,

and 365-day mortality by the Kaplan–Meier method. Conditional Cox proportional hazard regression was used to compute 1-year mortality rate ratio. The HR was controlled for sex, age, calendar year, and time since total colectomy by the matched study design.

Systemic Corticosteroid Exposure Before Total Colectomy

In secondary analyses, we evaluated preoperative systemic corticosteroid use within 90 days before or on the day of total colectomy as the primary exposure (see Supplementary Table 2 for codes). Patients were categorized into two groups: those with any systemic corticosteroid use and those without. We calculated the 30-day and 90-day absolute VTE risk with death as a competing risk. Subsequently, we estimated adjusted HRs comparing systemic corticosteroid use to no use. Models were adjusted for sex, age at colectomy, calendar year, admission type, surgical approach, colectomy type, preoperative length of stay, indication for colectomy, IBD duration, preoperative immunosuppressants, biologicals, and combination therapy, as well as comorbidity burden.

Results

Descriptive Characteristics

We identified 5303 patients with IBD undergoing total colectomy, among whom 1151 (22%) had CD and 4152 (78%) had UC. Baseline characteristics for patients with IBD undergoing total colectomy are summarized in Table 1. Patients with UC were slightly older at the time of surgery than those with CD (median [IQR] age: 43 [29–60] vs 40 [27–55] years). Most UC patients were men (53%), whereas most CD patients were women (57%). Emergency surgeries accounted for 47% of colectomies in CD and 57% in UC, with most procedures being open colectomies for both CD and UC (73% and 65%, respectively). The most common procedure was colectomy with ileostomy (66% in CD and 78% in UC). CRC was the indication for surgery in 4% of patients. Furthermore, approximately 9% of patients had a cancer diagnosis before total colectomy. Patients with CD had a longer disease duration before total colectomy than those with UC (median 5 vs 2 years). Preoperative IBD treatment was common (64% for CD and 82% for UC patients), most frequently corticosteroids or immunosuppressants. Most patients had a low comorbidity burden.

Risk and Hazard Ratios for Venous Thromboembolism

During follow-up, 15 CD patients and 82 UC patients developed VTE. Of these 97 VTE events, 25 (25.8%) were DVT, 52 (53.6%) were PE, and 20 (20.6%) were splanchnic vein thrombosis. Among patients with CD, the 0–30-day VTE risk after total colectomy was 0.6% and the 0–90-day VTE risk was 1.3% (Figures 1, 2, Supplementary Table 4 and Supplementary Figure 1). In patients with UC, the corresponding risks were 1.3% and 2.0%.

Figure 2 shows 30-day absolute risks for IBD overall and the corresponding adjusted hazard ratios (aHRs) for all potential risk factors. Of note, several estimates were imprecise due to low numbers of VTE events. During the 0–30-day follow-up period for IBD overall, the VTE rate was 1.6-fold higher in men than in women and increased with age (4.0-fold for ages 41–60 and 3.0-fold for ≥60 vs ≤40). The most recent calendar period showed a 3.8-fold higher rate than the earliest period (2014–2021 vs 1996–2001). Shorter IBD duration (<1 year vs 1–5 year) and corticosteroid treatment (yes vs no) were each associated with a higher rate (1.8-fold and 1.6-fold, respectively). The VTE rate was 2.1-fold higher in patients with high comorbidity than in those with low. Colectomy for colorectal cancer had a higher absolute 30-day risk than for medically refractory IBD, but the aHR was imprecise.

Associations were strongest in the first 30 days after total colectomy, with some attenuation during the 31–90 day follow-up period (Supplementary Figure 2).

Mortality After Venous Thromboembolism

Among the 97 patients who developed VTE after colectomy, 91 (six lacked comparators meeting the matching criteria) were matched to 284 IBD comparators without VTE. Within one year after the VTE event, 19 (21%) patients with VTE died compared with 11 (4%) deaths among comparators. In patients with VTE, mortality was 15.4% at 30 days, 16.5% at

Table 1 Characteristics of Patients with Inflammatory Bowel Disease Undergoing Total Colectomy, Denmark, 1996–2021

Characteristics	CD (N=1151, 100%)	UC (N=4152, 100%)	IBD Overall (N=5303, 100%)
Sex			
Male	497 (43.2%)	2187 (52.7%)	2684 (50.6%)
Female	654 (56.8%)	1965 (47.3%)	2619 (49.4%)
Age, years			
0–40	586 (50.9%)	1906 (45.9%)	2492 (47%)
41–60	339 (29.5%)	1190 (28.7%)	1529 (28.8%)
60+	226 (19.6%)	1056 (25.4%)	1282 (24.2%)
Median (IQR)	40 (27–55)	43 (29–60)	42 (28–59)
Year of surgery			
1996–2001	269 (23.4%)	891 (21.5%)	1160 (21.9%)
2002–2007	278 (24.2%)	975 (23.5%)	1253 (23.6%)
2008–2013	270 (23.5%)	1049 (25.3%)	1319 (24.9%)
2014–2021	334 (29%)	1237 (29.8%)	1571 (29.6%)
Admission type			
Elective	615 (53.4%)	1807 (43.5%)	2422 (45.7%)
Emergency	536 (46.6%)	2345 (56.5%)	2881 (54.3%)
Surgical approach			
Open colectomy	844 (73.3%)	2717 (65.4%)	3561 (67.2%)
Laparoscopic colectomy	307 (26.7%)	1435 (34.6%)	1742 (32.8%)
Type of colectomy			
Restorative proctocolectomy ± ileostomy	19 (1.7%)	300 (7.2%)	319 (6%)
Proctocolectomy with ileostomy	190 (16.5%)	401 (9.7%)	591 (11.1%)
Colectomy with ileostomy	760 (66%)	3249 (78.3%)	4009 (75.6%)
Colectomy with ileorectal anastomosis	143 (12.4%)	133 (3.2%)	276 (5.2%)
Other form of colectomy	39 (3.4%)	63 (1.5%)	102 (1.9%)
Proctocolectomy with Koch reservoir		6 (0.1%)	6 (0.1%)
Preoperative admission length, days			
0–3	697 (60.6%)	2336 (56.3%)	3033 (57.2%)
4–7	186 (16.2%)	673 (16.2%)	859 (16.2%)
>7	268 (23.3%)	1143 (27.5%)	1411 (26.6%)
Median (IQR)	2 (1–7)	3 (1–8)	3 (1–8)
Indication for colectomy			
CRC	38 (3.3%)	177 (4.3%)	215 (4.1%)
Medically refractory IBD	1113 (96.7%)	3975 (95.7%)	5088 (95.9%)
IBD duration, years			
<1	242 (21%)	1368 (32.9%)	1610 (30.4%)
1–5	337 (29.3%)	1326 (31.9%)	1663 (31.4%)
>5	572 (49.7%)	1458 (35.1%)	2030 (38.3%)
Median (IQR)	5 (1–11)	2 (1–8)	3 (1–9)
IBD treatment before surgery			
No treatment	353 (30.7%)	741 (17.8%)	1094 (20.6%)
Any treatment	798 (69.3%)	3411 (82.2%)	4209 (79.4%)
Corticosteroids	437 (38%)	2219 (53.4%)	2656 (50.1%)
Immunosuppressive Treatment	476 (41.4%)	2746 (66.1%)	3222 (60.8%)
Biological Treatment	279 (24.2%)	1108 (26.7%)	1387 (26.2%)
Combination Therapy	92 (8%)	773 (18.6%)	865 (16.3%)
Comorbidity burden[a]			
Low	737 (64%)	2725 (65.6%)	3462 (65.3%)
Medium	306 (26.6%)	1033 (24.9%)	1339 (25.2%)

(*Continued*)

https://doi.org/10.2147/CLEP.S590446

Table 1 (Continued).

Characteristics	CD (N=1151, 100%)	UC (N=4152, 100%)	IBD Overall (N=5303, 100%)
High	108 (9.4%)	394 (9.5%)	502 (9.5%)
Specific CCI conditions			
Myocardial Infarction	19 (1.7%)	108 (2.6%)	127 (2.4%)
Congestive Heart Failure	29 (2.5%)	78 (1.9%)	107 (2%)
Peripheral Vascular Disease	34 (3%)	91 (2.2%)	125 (2.4%)
Cerebrovascular Disease	31 (2.7%)	168 (4%)	199 (3.8%)
Dementia	5 (0.4%)	16 (0.4%)	21 (0.4%)
Chronic Pulmonary Disease	114 (9.9%)	354 (8.5%)	468 (8.8%)
Connective Tissue Disease	50 (4.3%)	140 (3.4%)	190 (3.6%)
Ulcer Disease	57 (5%)	105 (2.5%)	162 (3.1%)
Mild Liver Disease	39 (3.4%)	86 (2.1%)	125 (2.4%)
Diabetes I And Ii	51 (4.4%)	229 (5.5%)	280 (5.3%)
Hemiplegia	<5	≥5	17 (0.3%)
Moderate To Severe Renal Disease	33 (2.9%)	81 (2%)	114 (2.1%)
Diabetes With End Organ Damage	26 (2.3%)	79 (1.9%)	105 (2%)
Any Tumor	91 (7.9%)	377 (9.1%)	468 (8.8%)
Leukemia	<5	≥5	10 (0.2%)
Lymphoma	11 (1%)	18 (0.4%)	29 (0.5%)
Moderate To Severe Liver Disease	8 (0.7%)	28 (0.7%)	36 (0.7%)
Metastatic Solid Tumor	5 (0.4%)	48 (1.2%)	53 (1%)
Aids	<5	≥5	8 (0.2%)
Atrial Fibrillation Flutter	37 (3.2%)	145 (3.5%)	182 (3.4%)
Obesity	68 (5.9%)	202 (4.9%)	270 (5.1%)

Notes: [a]Based on Charlson Comorbidity Index scores (low: score of 0, medium: score of 1–2, high: score ≥3). We modified the Charlson Comorbidity Index (CCI) to exclude any previous colorectal cancer and include codes for atrial fibrillation/flutter and obesity.
Abbreviations: CCI, Charlson Comorbidity Index; CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; IQR, interquartile range; VTE, venous thromboembolism; UC, ulcerative colitis.

90 days, and 21.0% at one year (Figure 3). Mortality in comparators without VTE was <1% at 30 days and increased to 3.9% at one year (Figure 3). The one-year hazard ratio associating VTE with death was 7.65 (95% CI, 3.12–18.73).

Systemic Corticosteroid Use and Risk of Venous Thromboembolism

Among the 5303 patients who underwent total colectomy, 2147 (40%) received systemic corticosteroids. Baseline characteristics based on preoperative systemic corticosteroid use are shown in Supplementary Table 5. The 30-day and 90-day absolute risks of VTE were 1.5% and 2.4% among patients who received preoperative systemic corticosteroids, compared with 0.9% and 1.5% among those who did not (Supplementary Figure 3 and Supplementary Table 6). During the 0–30-day period, preoperative systemic corticosteroid use was associated with a 2.1-fold higher rate of postoperative VTE than no use (Figure 4). During this period, the highest rates were observed among patients with UC (2.2-fold), among men (2.1-fold), and among patients aged 41–60 years (3.6-fold). Higher VTE rates associated with corticosteroid use were also observed in the most recent calendar period (2.5-fold), for elective surgery (2.2-fold), laparoscopic colectomy (2.6-fold), preoperative admission >7 days (2.7-fold), IBD duration <1 year (2.5-fold), preoperative immunosuppressive treatment (2.2-fold), biologic treatment (5.1-fold), and medium comorbidity burden (4.8-fold) (Figure 4). The associations attenuated during the 31–90-day period (Supplementary Figure 4).

Discussion

In this population-based cohort study of patients with IBD undergoing total colectomy, we found that age (40–60 and 60+ years), recent calendar year, recent diagnosis of IBD, high comorbidity burden, use of corticosteroids, and male sex were

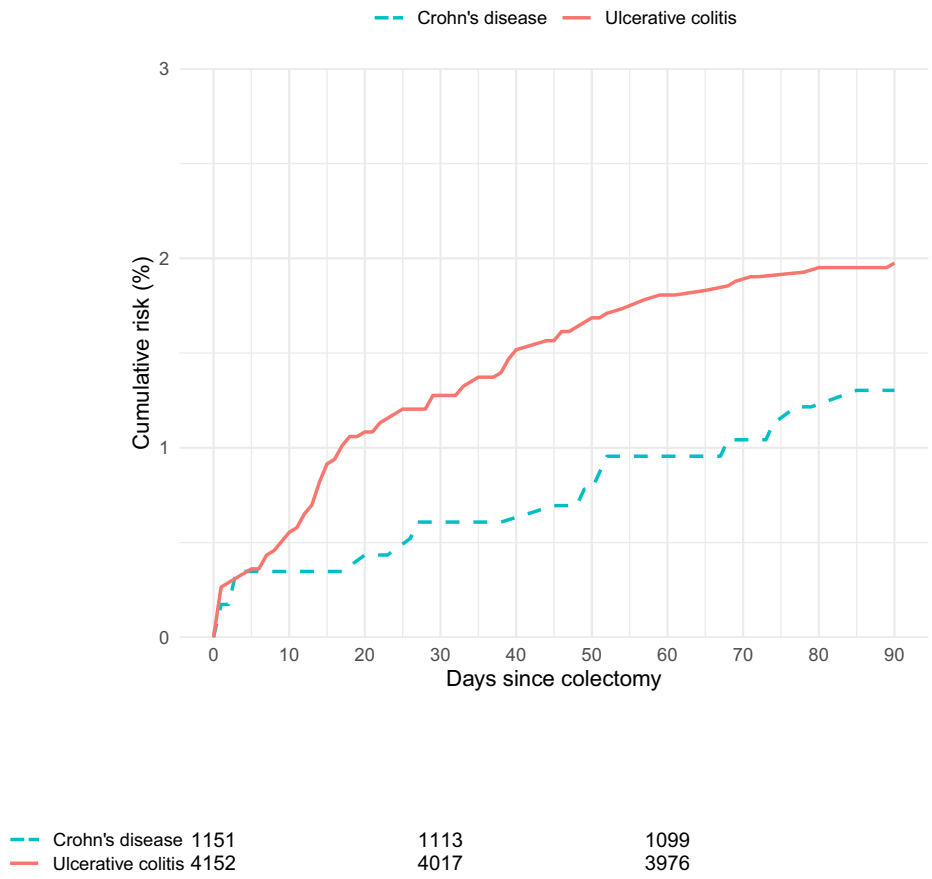

Figure 1 Risk of venous thromboembolism at 0–90 days post-surgery in patients with inflammatory bowel disease undergoing total colectomy in Denmark, 1996–2021.

potential risk factors for VTE. The strongest associations were observed during the first 30 days post-surgery. Most importantly, we found that VTE after total colectomy was associated with substantial increased mortality. Systemic corticosteroid use within 90 days before colectomy was associated with an approximately twofold higher 30-day rate of VTE compared to no use.

Our study adds to the existing evidence by focusing specifically on total colectomy, providing procedure-specific estimates of VTE risk and associated risk factors in a population already at high risk of thrombosis. Our findings mirror those from studies of pooled colorectal procedures, where older age, corticosteroid use, comorbidity burden, and ulcerative colitis (UC) diagnosis have consistently been identified as important risk factors for postoperative VTE.[5,7–11,36–38] We observed similar associations in our total colectomy cohort, which strengthens the evidence that these characteristics are important determinants of thrombotic risk. Interestingly, our study identified two risk factors that have not been emphasized in previous research. First, we observed that the risk of VTE increased in more recent calendar years, despite advances in prophylaxis protocols and perioperative management. A potential explanation is enhanced case ascertainment driven by more sensitive diagnostic imaging, greater clinical awareness, and improved coding, which may have increased the number of recorded VTE events. Another possibility is that colectomy is increasingly performed for patients with complicated or refractory IBD,[1] who are inherently at higher thrombotic risk. Finally, although extended prophylaxis use may have increased over time, current guidelines recommend considering extended thromboprophylaxis only for selected high-risk IBD patients, without clearly defining what constitutes high risk.[19,20] In addition, even with broader adoption of extended prophylaxis, a residual risk of VTE persists.[39] Second, we found that a shorter duration of IBD before surgery was associated with a higher risk of postoperative VTE. One explanation is that patients who need colectomy early in their disease may have aggressive or treatment-refractory IBD, and their acute inflammatory burden at the time of surgery might increase their susceptibility to thromboembolic events. This finding is also consistent with the

Characteristics	VTE risk, % (95% CI)	aHR (95% CI)
IBD subtype		
CD	0.6 (0.2–1.1)	Reference
UC	1.3 (0.9–1.6)	1.81 (0.74–4.44)
Sex		
Female	1.4 (1.0–1.9)	Reference
Male	0.8 (0.5–1.2)	1.56 (0.92–2.64)
Age, years		
0–40	0.4 (0.2–0.6)	Reference
41–60	1.8 (1.1–2.4)	3.95 (1.87–8.37)
60+	1.8 (1.1–2.5)	2.96 (1.30–6.75)
Year of surgery		
1996–2001	0.4 (0.1–0.8)	Reference
2002–2007	1.0 (0.5–1.6)	2.23 (0.69–7.16)
2008–2013	1.1 (0.5–1.6)	2.95 (0.90–9.68)
2014–2021	1.8 (1.1–2.4)	3.84 (1.10–13.34)
Admission type		
Elective	0.9 (0.6–1.3)	Reference
Emergency	1.3 (0.9–1.7)	1.10 (0.52–2.34)
Surgical approach		
Laparoscopic	1.3 (0.8–1.9)	Reference
Open colectomy	1.0 (0.7–1.4)	1.15 (0.56–2.36)
Type of colectomy		
Colectomy with ileorectal anastomosis	0.7 (0.0–1.7)	Reference
Colectomy with ileostomy	1.2 (0.9–1.6)	0.93 (0.22–3.98)
Proctocolectomy with ileostomy	1.2 (0.3–2.1)	1.25 (0.25–6.09)
Restorative proctocolectomy ± ileostomy	0.3 (0.0–0.9)	0.00 (−)
Proctocolectomy with Koch reservoir	0.0 (0.0–0.0)	0.00 (−)
Other form of colectomy	1.0 (0.0–2.9)	1.44 (0.13–16.21)
Preoperative admission length, days		
0–3	1.0 (0.6–1.3)	Reference
4–7	1.2 (0.4–1.9)	0.78 (0.29–2.07)
>7	1.4 (0.8–2.0)	1.59 (0.75–3.40)
Indication for colectomy		
Medically refractory IBD	1.1 (0.8–1.3)	Reference
CRC	2.8 (0.6–5.0)	1.19 (0.33–4.27)
IBD duration, years		
1–5	0.7 (0.3–1.1)	Reference
<1	1.6 (0.9–2.2)	1.84 (0.81–4.16)
>5	1.2 (0.7–1.7)	1.55 (0.69–3.47)
Any IBD treatment		
No treatment	0.8 (0.3–1.4)	Reference
Any treatment	1.2 (0.9–1.5)	1.24 (0.58–2.63)
Corticosteroids		
No	0.8 (0.5–1.2)	Reference
Yes	1.4 (1.0–1.9)	1.55 (0.86–2.79)
Immunosuppressive treatment		
No	1.2 (0.7–1.6)	Reference
Yes	1.1 (0.8–1.5)	0.98 (0.54–1.77)
Biological treatment		
No	1.0 (0.7–1.4)	Reference
Yes	1.4 (0.8–2.0)	1.09 (0.54–2.23)
Combination therapy		
No	1.1 (0.8–1.4)	Reference
Yes	1.4 (0.6–2.2)	1.30 (0.62–2.73)
Comorbidity burden [a]		
Low	0.8 (0.5–1.1)	Reference
Medium	1.3 (0.7–1.9)	1.03 (0.49–2.16)
High	3.2 (1.7–4.7)	2.14 (0.94–4.88)

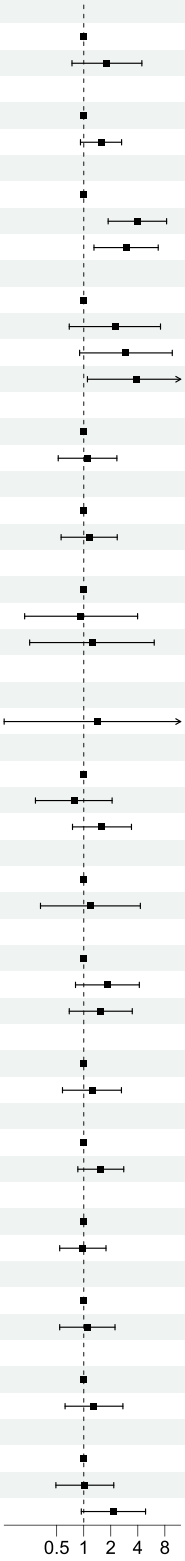

Figure 2 Analysis of risk factors for venous thromboembolism in patients with inflammatory bowel disease 0–30-days after total colectomy in Denmark.

Notes: Hazard ratios were adjusted for sex, age, year of total colectomy, admission type, surgical approach, colectomy type, preoperative length of stay, colectomy indication, IBD duration, IBD medical treatment, and comorbidity burden. [a]Based on Charlson Comorbidity Index (CCI) scores (low: score of 0, medium: score of 1–2, high: score ≥3). The CCI was modified to exclude any previous colorectal cancer and include codes for atrial fibrillation/flutter and obesity.

Abbreviations: aHR, adjusted hazard ratio; CCI, Charlson Comorbidity Index; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis; VTE, venous thromboembolism.

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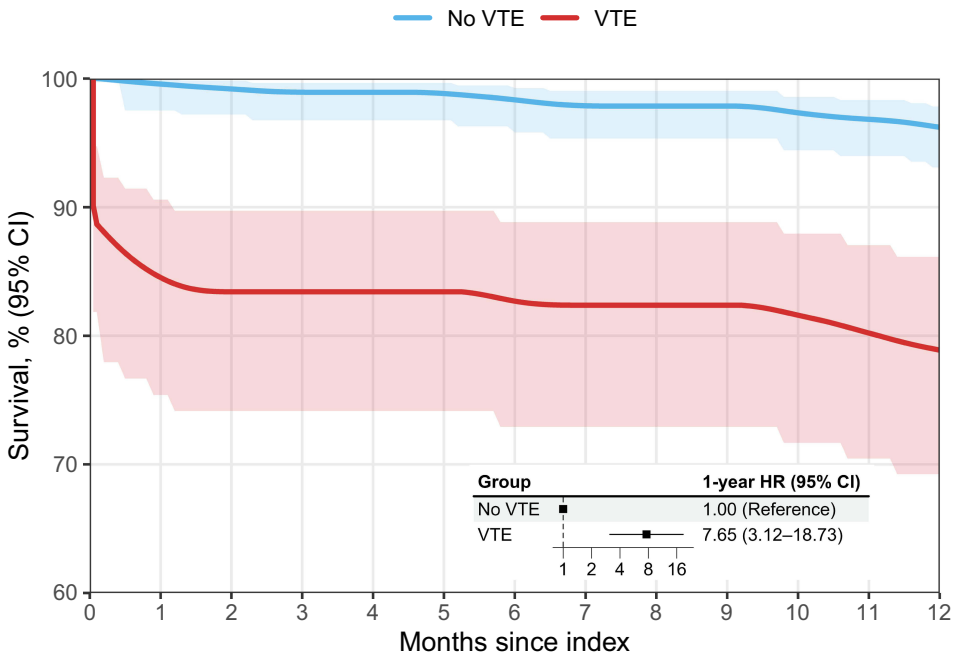

Figure 3 One-year survival and hazard ratio for patients with venous thromboembolism event within 90 days after total colectomy and matched comparators.
Notes: Patients were followed from a VTE outcome (index date for comparators) until 1 year of follow-up, death, or the end of the study (December 31, 2021), whichever came first. The Kaplan–Meier estimator was used to estimate 1-year mortality. The hazard ratio was controlled for age, sex, and the calendar year of total colectomy by design.
Abbreviations: CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

possibility that the higher VTE rates observed in more recent calendar periods partly reflect a greater proportion of patients undergoing colectomy for more severe or treatment-refractory disease.

Age has been repeatedly described as a key risk factor, with earlier studies mainly emphasizing patients more than 65 years old.[5] However, our study showed the strongest association among patients aged 40–60 years. This relatively young group is often assumed to have a lower vascular risk, but our results suggest that postoperative VTE remains a significant complication even in middle-aged individuals. A likely explanation is that active IBD and the systemic inflammatory response from colectomy can promote thrombosis regardless of age, highlighting that careful attention to prophylaxis is necessary even in middle-aged patients.

While previous studies reported emergency surgery and open surgical approach as important risk factors for VTE,[5,9,11,36,37] we did not observe such associations in our analysis restricted to total colectomy. One possible explanation is that total colectomy represents such a high-risk procedure for VTE that the impact of surgical urgency and operative approach becomes less pronounced. Therefore, whether performed electively or emergently, open or laparoscopic, the baseline risk of thrombosis may remain elevated. Differences in thromboprophylaxis practices between elective and emergency procedures, and between laparoscopic and open surgery, may also have contributed to the observed associations. Unfortunately, we were unable to examine this further because we lacked data on thromboprophylaxis with LMWH. Another explanation is that the definitions of emergency surgery might have varied across studies. In our analysis, emergency status was based on admission type and whether the surgery took place during that admission. In contrast, other studies might have used operative reports or surgeon designation, which could contribute to inconsistent findings.

We also found that a substantial number of total colectomies were performed for colorectal cancer, showing a high absolute risk of VTE. This finding is consistent with a recent study showing elevated VTE rates in IBD patients undergoing colorectal cancer surgery,[40] which may reflect cancer-associated hypercoagulability and thrombotic mechanisms specific to the coexistence of IBD and colorectal cancer, distinct from those associated with either condition alone.[41–44]

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Characteristics	aHR (95% CI)
VTE no corticosteroid treatment	Reference
VTE corticosteroid treatment overall	2.06 (1.20–3.53)
IBD subtype	
CD	0.95 (0.17–5.35)
UC	2.22 (1.24–3.96)
Sex	
Female	1.62 (0.70–3.74)
Male	2.07 (1.08–3.94)
Age, years	
0–40	1.32 (0.38–4.55)
41–60	3.56 (1.59–7.93)
60+	1.22 (0.54–2.79)
Year of surgery	
1996–2001	2.23 (0.37–13.38)
2002–2007	1.22 (0.41–3.65)
2008–2013	1.66 (0.58–4.75)
2014–2021	2.49 (1.16–5.31)
Admission type	
Elective	2.19 (0.96–5.01)
Emergency	1.71 (0.89–3.27)
Surgical approach	
Laparoscopic colectomy	2.64 (1.12–6.24)
Open colectomy	1.55 (0.81–2.96)
Type of colectomy	
Restorative proctocolectomy ± ileostomy	0.00 (−)
Proctocolectomy with Koch reservoir	0.00 (−)
Proctocolectomy with ileostomy	2.97 (0.66–13.43)
Colectomy with ileostomy	1.57 (0.90–2.76)
Colectomy with ileorectal anastomosis	0.00 (−)
Other form of colectomy	0.00 (−)
Preoperative admission length, days	
0–3	1.54 (0.75–3.15)
4–7	1.97 (0.55–7.06)
>7	2.73 (1.12–6.68)
Indication for colectomy	
Medically refractory IBD	1.81 (1.06–3.09)
CRC	5.54 (1.03–29.89)
IBD duration, years	
1–5	1.16 (0.35–3.83)
<1	2.49 (1.09–5.69)
>5	1.78 (0.80–3.96)
Immunosuppressive treatment	
No	1.68 (0.73–3.87)
Yes	2.15 (1.07–4.30)
Biological treatment	
No	1.27 (0.68–2.36)
Yes	5.06 (1.68–15.28)
Combination therapy	
No	1.42 (0.80–2.50)
Yes	12.14 (1.57–94.11)
Comorbidity burden [a]	
Low	1.43 (0.67–3.05)
Medium	4.84 (1.58–14.86)
High	1.38 (0.51–3.73)

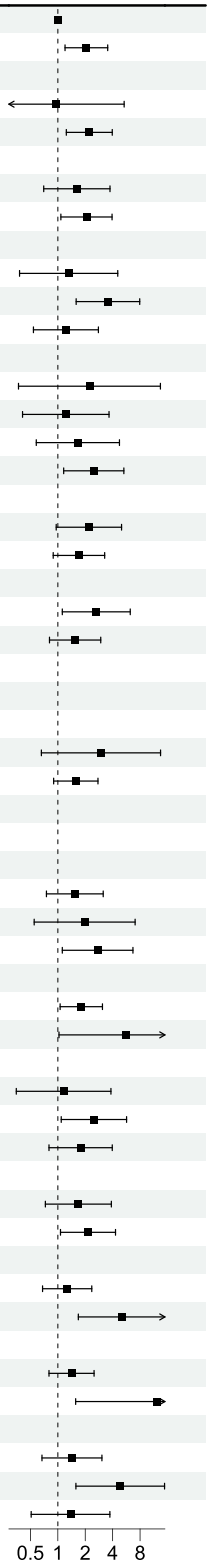

Figure 4 Hazard ratios with 95% confidence intervals associating corticosteroid use with risk of venous thromboembolism in patients with inflammatory bowel disease who underwent total colectomy, during 0–30-day follow-up.

Notes: Hazard ratios were adjusted for sex, age, year of total colectomy, admission type, surgical approach, colectomy type, preoperative length of stay, colectomy indication, IBD duration, immunosuppressive treatment, biological treatment, combination therapy, and comorbidity burden. [a]Based on Charlson Comorbidity Index (CCI) scores (low: score of 0, medium: score of 1–2, high: score ≥3). The CCI was modified to exclude any previous colorectal cancer and include codes for atrial fibrillation/flutter and obesity.

Abbreviations: aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis; VTE, venous thromboembolism.

To date, only two studies have reported mortality following VTE after colorectal surgery in patients with IBD.[9,39] However, these studies had several methodological limitations. Most importantly, because the studies did not provide information on the time from surgery to VTE, how the association between VTE and mortality was established remained unclear. Without this information, immortal time bias was likely introduced, thus leading to an underestimation of the true mortality burden. In our study, we addressed this by using a matched risk-set design in which mortality follow-up began at the date of VTE for cases and at the equivalent postoperative time point for matched comparators. Although our findings are broadly consistent with previous reports, our design may provide a less biased estimate of the mortality burden associated with postoperative VTE.

The observed association between systemic corticosteroid use and early postoperative VTE is biologically plausible. Systemic corticosteroids can promote thrombosis through their effects on coagulation,[45] and they are often prescribed during periods of high disease activity.[46] In patients with IBD undergoing major colorectal surgery, systemic inflammation, surgical trauma, immobilization, and corticosteroid therapy may therefore coincide, leading to substantial transient hypercoagulability. The stronger associations observed in patients receiving intensive IBD treatment in our study should be interpreted with caution given the limited precision, but they align with the notion that systemic corticosteroid use indicates a subgroup of patients with severe, active disease. This may also help explain the stronger association observed in elective surgery, as elective status does not preclude persistent inflammatory burden or treatment-refractory disease despite the opportunity for preoperative optimization.

The strengths of our study include its nationwide, population-based design with universal healthcare coverage, complete follow-up, and the use of high-quality registry data for exposures, outcomes, and covariates.[22,26,28,34] Several limitations should also be acknowledged. The overall number of VTE events was modest, leading to imprecision in some hazard ratio estimates and preventing more detailed analyses by IBD subtype or type of VTE. The small number of events also limited our ability to adjust for multiple individual comorbidities and medication exposures that could influence VTE risk. Therefore, we summarized comorbidity burden using a modified CCI that also included atrial fibrillation/flutter and obesity. However, this approach may not fully capture the complexity of specific comorbid conditions and related treatments, and residual confounding cannot be excluded. Furthermore, disease activity, which is associated with VTE risk,[17] could not be directly measured in our study. Registry-based proxies for disease activity are difficult to define in patients undergoing colectomy, and variables such as disease duration, preoperative admission length, and admission type likely reflect only part of the inflammatory burden at the time of surgery. In addition, CD was classified using registry-based diagnostic codes, so we were unable to distinguish Crohn's colitis from other CD phenotypes or characterize extraintestinal disease involvement. Information on hospital-administered pharmacological prophylaxis, such as LMWH, is not systematically captured in Danish registries because it may be provided during hospitalization or supplied by the hospital for perioperative use after discharge. This limitation may influence the interpretation of early postoperative risk in relation to existing prophylaxis guidelines. Moreover, we lacked information on certain lifestyle-related confounders, including smoking status and body weight, which may have affected risk estimates. Finally, although the matched risk-set design reduced immortal time bias in the mortality analysis, residual confounding cannot be excluded. The limited number of deaths also restricted adjustment beyond the matching factors, which may have influenced the estimates.

Conclusion

In conclusion, our results suggest that older age, recent calendar year, recent diagnosis of IBD, high comorbidity burden, use of corticosteroids, and male sex may be associated with particularly high risks of VTE after total colectomy for IBD. These findings may help identify subgroups where awareness should be heightened and where targeted strategies could be explored in future research. Furthermore, our observation that postoperative VTE is associated with increased mortality reinforces the clinical importance of prevention and timely detection. While our study cannot determine optimal prophylaxis strategies or disentangle the independent effect of corticosteroids from the underlying disease severity, the findings emphasize the need for future research to evaluate extended prophylaxis in high-risk IBD patients and may help guide the development of personalized perioperative care and future guideline updates.

Abbreviations

aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; IQR, interquartile range; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UC, ulcerative colitis; VTE, venous thromboembolism.

Data Sharing Statement

The individual-level data used for this study are not publicly available, but can be obtained by application to Statistics Denmark (https://www.dst.dk/en/TilSalg/Forskningsservice/Dataadgang).

Ethics Approval Statement

The study was conducted using administrative register data. According to Danish law, ethical approval is not required for such research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

None of the authors have any disclosures relevant to this study.

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