

High Incidence of Postoperative Silent Venous Thromboembolism in Ulcerative Colitis

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Abstract

Purpose: The incidence of postoperative venous thromboembolism (VTE) is high in patients with inflammatory bowel diseases. We aimed to analyze the incidence and predictive factors of postoperative VTE.

Methods: Patients with ulcerative colitis who underwent colon and rectum surgery during 2010–2018 were included. We retrospectively investigated the incidence of postoperative VTE.

Results: A total 140 cases of colorectal surgery were included. Postoperative VTE was detected in 24 (17.1%). All patients with VTE had no specific symptoms related to thrombus, except one pulmonary embolism. Portal–mesenteric venous thrombosis was the most frequent (18, 75%); of these, 15 patients underwent total proctocolectomy (TPC) with ileal pouch–anal anastomosis (IPAA). In univariate analysis, VTE occurred more frequently in patients with neoplasia than refractory to medications (27.2% vs. 12.5%; $p < 0.031$). TPC with IPAA was more associated with developing VTE (28%) than total colectomy (10.5%) or proctectomy (5.9%). On logistic regression analysis of predictive risk factors, TPC with IPAA, total colectomy, longer operative time (>4 hours), and high serum D-dimer levels (>5.3 $\mu\text{g/mL}$) the day following surgery were identified.

Conclusion: Postoperative VTE occurred frequently and asymptomatic, especially after TPC with IPAA. D-dimer the day after surgery may be useful predictor of VTE.

Introduction

Venous thromboembolism (VTE) is a well-known complication after colorectal surgery, which causes morbidity and mortality in hospitalized as well as discharged patients. In particular, patients with ulcerative colitis (UC) show a higher incidence of VTE postoperatively.

Current guidelines from the American Society of Colon and Rectal Surgeons recommend pharmacological prophylaxis with low-dose unfractionated heparin or low-molecular-weight heparin in patients with moderate and high risk following abdominal surgery. Patients with inflammatory bowel disease (IBD) are defined as having a high risk for VTE [1].

Despite many reports on postoperative VTE and guidelines recommending pharmacological prophylaxis, this is not sufficiently administered in clinical practice. There might be some reasons, the risk of postoperative bleeding from remnant rectum with acute flare, epidural hematoma, and mostly surgeon's low recognition of postoperative VTE.

Many previous studies on VTE have been conducted in Western countries, and these have reported that the risk of postoperative VTE is 2- to 3-fold higher in patients with UC, with rates of VTE of 4.1–5.8% [2] [3].

We suspect that more postoperative VTE occur in patients with UC in our clinical setting than the findings of previous reports. As the data in past studies were extracted from large nationwide databases, these are considered reliable and there is less likelihood of bias in such large datasets. However, it is possible that only patients with symptomatic VTE were registered and that many patients with asymptomatic VTE were not included in those data. We therefore conducted a retrospective study of postoperative VTE in patients with UC in IBD-specialized facilities of Japan and reviewed all computed tomography (CT) scans that had been examined postoperatively. The aim of this study was to clarify the incidence of postoperative VTE including the asymptomatic thrombus and to identify predictive factors for VTE.

Materials And Methods

Data collection and variables

We performed this retrospective observational study using a prospectively maintained database of patients with UC undergoing abdominopelvic bowel resection at Hiroshima University Hospital between January 2010 and December 2018. In total, we included 143 operation cases among 110 patients. Among these cases, we excluded three cases of total colectomy (TC) with preoperative VTE (Fig. 1). Restorative proctocolectomy and proctectomy were conducted with rectal mucosectomy and hand-sewn pouch–anal anastomosis with a J pouch. We reviewed patients' electronic medical charts to obtain information regarding patient characteristics, surgical procedures, and postoperative data. Emergency surgery was defined as an unplanned surgery on admission. The preoperative state of venous thrombosis was assessed using contrast-enhanced CT, the image range was from chest to pelvic, just prior to emergency surgery, and within at least 4 weeks of elective surgery. All patients underwent early mobilization on the day following surgery and used mechanical VTE prophylaxis, with compression stockings and an intermittent pneumatic compression device, from the time of surgery until the start of walking. As pharmacological prophylaxis, low molecular heparin or unfractionated heparin was used for 7 days after surgery, and administration was decided by surgeons.

Outcome

The primary outcome was incidence of in-hospital VTE after abdominopelvic surgery. The secondary outcome was predictive risk factors for venous thrombosis.

In this study, VTE included pulmonary embolism (PE), deep vein thrombosis (DVT), and portal–mesenteric venous thrombosis (PMVT). DVT included thrombosis at the vena cava, internal jugular vein, subclavian vein, and femoral vein. Diagnosis of VTE was assessed using contrast-enhanced CT examination as well as supplementary ultrasound examination. The preoperative therapy included use of steroid just prior to surgery, immunosuppressive agents within 1 week before surgery, and biological agents within 6 weeks prior to surgery.

Statistical analysis

Analysis was conducted with JMP version 11 (SAS Institute Japan Ltd., Tokyo, Japan). Statistics are reported as median with interquartile range (IQR) for continuous variables and frequency with percentage for categorical variables. Normally distributed continuous variables were analyzed using the *t*-test, and nonnormally distributed continuous variables were analyzed with the nonparametric Wilcoxon's rank-sum test. Fisher's exact test was performed for categorical variables. Multivariable logistic regression analysis was conducted to identify predictive risk factors for surgical recurrence at the anastomosis site. Each analysis was performed using a two-sided 5% significance level and 95% confidence interval.

Ethical considerations

This study was approved by the Hiroshima University institutional review board (E-1636). Participants received information about the conduct of the research, including the purpose of the study, and were given the opportunity to decline participation in the study. Because the opt-out method can be used without informed consent from the patient, it was published on the web.

Results

We included a total 110 patients with UC in this study. The total number of operations was 143 cases, including 64 cases of TPC with IPAA, 40 cases of TC with ileostomy, 34 cases of proctectomy with IPAA, 4 cases of partial colectomy, and one case of TC with ileorectal anastomosis. Three patients with TC who had preoperative VTE were excluded from the analysis (Fig. 1). Of these 140 cases, postoperative VTE was detected in 24 cases (17.1%) at 7 (5.2–9.7) days after surgery.

Contrast-enhanced CT after surgery was conducted in 91 cases (65%). The most frequent reason for CT examination were suspicion of pelvic abscess or outlet obstruction at the stoma site with elevated fever, abdominal pain, and ileus. Eighteen cases (12.8%) with elevated serum D-dimer levels or transaminase were suspected of VTE prior to CT examination, and VTE was detected in 5 cases of those. All patients with VTE after surgery had no specific symptoms related to VTE, except for one patient who had pulmonary embolism with dyspnea on walking.

Regarding the site of thromboembolism, PMVT occurred most frequently (18 patients, 75%). Of those, 15 patients were detected after TPC + IPAA (Fig. 2). All 17 cases of liver portal vein thrombosis were detected in the right hepatic lobe, and 5 of these cases showed mesenteric venous thrombosis simultaneously. With respect to mesenteric venous thrombosis, five cases were in the inferior mesenteric vein, 2 cases in the superior mesenteric vein, and one case was in the splenic vein. PE occurred in four cases (2.8%, three cases after TPC + IPAA, and one case after TC). One subclavian vein thrombus and one jugular vein thrombus was detected after TC.

The rate of postoperative VTE prophylaxis with anticoagulant was 31.4% in all patients, 41.7% in the VTE (+) group and 29.3% in the VTE (-) group, respectively. The surgical procedure was TPC + IPAA 28 cases (43.7%), TC in 6 cases (16.2%), and proctectomy with IPAA in 10 cases (29.4%).

On univariate analysis, VTE occurred more frequently in patients with neoplasia (cancer or high-grade dysplasia) than refractory to medications (27.2% vs. 12.5%; $p < 0.031$). There was no difference in age, body mass index, American Society of Anesthesiology-physical status (ASA-PS) score ≥ 3 , current smoking, preoperative therapy, and comorbidity between the VTE (+) group and VTE (-) group (Table 1). The perioperative results showed significant differences in the rates of VTE according to surgical procedure. Patients who underwent TPC with IPAA were more likely to develop VTE (28%) than TC (10.5%) or proctectomy (5.9%). Operative time in the VTE (+) group was significantly longer than in the VTE (-) group (340 vs. 291 minutes, $p = 0.006$). Laboratory data indicated that serum D-dimer levels on the day following surgery were higher in the VTE (+) group (5.6 $\mu\text{g/mL}$ vs. 3.1 $\mu\text{g/mL}$, $p = 0.00218$). D-dimer at day 3 after surgery was also higher in the VTE (+) group, but this was not significantly different (Table 2).

Table 1
Patient characteristics according to venous thromboembolism

	overall	VTE +	VTE -	<i>p</i> value
	N = 140	N = 24	N = 116	
Gender, n (%)				
Male	97 (69.3)	15 (62.5)	82 (70.6)	0.428
Female	43 (31.7)	9 (37.5)	34 (29.3)	
Age, median (range)	54 (41.2–63)	48 (38.2–57.5)	55.5 (42–64.7)	0.158
BMI, median (range)	21 (18.7–24.1)	21.8 (18.4–24)	20.5 (18.7–24.1)	0.81
ASA-PS \geq 3, n (%)	8 (5.7)	1 (4.2)	7 (6.0)	0.719
Current smoking, n (%)	13 (9.3)	2 (8.3)	11 (9.48)	0.86
Preoperative therapy, n (%)				
Steroid	59 (42.1)	13 (54.2)	46 (39.6)	0.19
Immunosuppressive agents	48 (34.2)	9 (37.5)	39 (33.6)	0.72
Biological agents	20 (14.2)	3 (12.5)	17 (14.7)	0.78
Comorbidity, n (%)				
HT	20 (14.2)	5 (20.8)	15 (8.6)	0.31
HL	11 (7.9)	1 (4.2)	10 (8.6)	0.46
DM	15 (10.7)	0	15 (12.9)	0.073
Indication, n (%)				
cancer/ dysplasia	44 (31.4)	12 (50)	32 (27.5)	
refractory to medication	96 (68.5)	12 (50)	84 (87.5)	*0.0313
Abbreviations: VTE, venous thromboembolism; BMI, body mass index; ASA-PS, American Society of Anesthesiology-physical status; HT, hypertension; HL, hyperlipidemia; DM, diabetes mellitus.				

Table 2
Peri-operative results according to venous thromboembolism

	overall	VTE +	VTE -	<i>p</i> value
	N = 140	N = 24	N = 116	
Procedure				
TPC+IPAA, n (%)	64 (45.7)	18(75)	46 (39.7)	
TC, n (%)	38 (27.1)	4 (16.7)	34 (29.3)	
Proctectomy + IPAA, n (%)	34 (24.2)	2 (8.3)	32 (27.6)	
Other, n (%)	4 (2.8)	0	4 (3.4)	*0.0144
IPAA	96 (68.6)	20 (83.3)	76 (65.5)	0.087
Operative time, min.(range)	291 (203–383)	340 (255–476)	277 (181–355)	*0.006
Blood loss, ml (range)	300 (155–522)	326 (230–528)	275 (12–520)	0.1775
Complications				
Ileus, n (%)	28 (20)	6 (25)	22 (19)	0.57
Anastomosis leakage, n (%)	9 (6.4)	1 (4.2)	8 (6.9)	0.629
Pelvic abscess, n (%)	24 (17)	3 (12.5)	21 (18)	0.497
Emergency operation	36 (27.6)	5 (20.8)	31 (26.7)	0.5478
Prophylaxis with anticoagulant, n (%)	44 (31.4)	10 (41.7)	34 (29.3%)	0.2956
D-dimer, µg/ml (range)				
POD1 D-dimer,	3.1 (2.2–5.8)	5.6 (2.7–8.9)	3 (2.2–4.7)	*0.0218
POD3 D-dimer	4.4 (3.1–8.25)	7 (3.5–10.6)	4.1 (3.1–7.7)	0.083
Peak D-dimer	8.85 (5.9–13)	10.1 (7.4–15.3)	8.7 (5.7–12)	0.072
Abbreviations: VTE, venous thromboembolism; TPC, total proctocolectomy; IPAA, ileal pouch–anal anastomosis; TC, total colectomy; POD, post-operative day.				

In logistic regression analysis, we identified that TPC with IPAA, TC, longer operative time (> 4 hours), and serum D-dimer level > 5.3 mg/dL on the day following surgery were predictive risk factors for postoperative VTE in patients with UC (Table 3).

Table 3
Predictive risk factors in logistic regression analysis

		OR	95% CI	<i>p</i> value
Procedure	Proctectomy + IPAA	reference	-	-
	TC	45.88	1.44–2863	*0.0304
	TPC + IPAA	17.12	1.675–433.7	*0.015
Indication	cancer/dysplasia	0.45	0.06–2.89	0.405
Operative time	(> 4 h)	28.84	1.23–1260	*0.0358
D-dimer at Day1	(> 5.3 µg/dl)	3.69	1.02–14.78	*0.0452
Abbreviations: OR, odds ratio; CI, confidence interval; TPC, total proctocolectomy; IPAA, ileal pouch–anal anastomosis; TC, total colectomy.				

Discussion

In this study, postoperative VTE in patients with UC was detected in 24 cases (17.1%) at a median 7 days after surgery. PMVT was the most common site of VTE (18 cases, 12.8%), and that was occurred frequently after TPC with IPAA (23.4%). Three predictive risk factors detected in logistic regression analysis (Table 3) were elevated D-dimer on the day after surgery, surgical procedure (TPC with IPAA, TC) and long operation time (over 4 hours).

IBD is a well-known independent risk factor for VTE, and patients with UC have higher risk of VTE than those with Crohn's disease [3] [4]. In patients with IBD, the risk of developing DVT and PE was 1.98- and 1.80-fold higher than other individuals, and the rates of postoperative VTE were 2.5–3.8%, which was higher than the 2.4% among patients with colorectal cancer [5–9]. The incidence rate of VTE in our study (17.1%) was higher than previous reports. One of the reasons is that our study was including asymptomatic VTE. CT examination after surgery was conducted for 91 cases (65%), and many asymptomatic venous thrombus were coincidentally identified. It's only 5 cases those were suspected of VTE before CT, and other 19 cases were coincident. Frequent postoperative CT might be related with Universal Insurance System for all people in Japan, which allow us to use informative CT easily in order to detect the postoperative complications.

PMVT was frequently detected after TPC + IPAA in our study. There are few studies regarding PMVT. The reported rate of symptomatic PMVT after colorectal surgery is 2.9–4.9% [10, 11] [12]. IBD is a frequent cause of PMVT after abdominal surgery, with a reported rate of 8.3% [13]. As a surgical procedure, restorative TPC with IPAA for patients with UC has been reported as an independent predictor of PMVT, and the incidence rate was as high as 5.8–10% [14] [11, 15] [16]. In the procedure of ileal pouch construction and anal anastomosis, there were several factors to promote thrombus in addition to the nature of IBD. Those were long operation time, pelvic surgery in the lithotomy position, manipulation of

mesenteric vessels, and traction of the superior mesentery vessels related to IPAA reconstruction. Dehydrated state caused by covering ileostomy was also related to thrombosis, which was created for every patient at our institution.

D-dimer elevation (> 5.3 mg/dL) a day after surgery was detected as predictive risk factor for postoperative VTE in this study, and the sensitivity was 55%, and the specificity was 78.5%. D-dimer is not specific marker only for thrombus. Disease flares, bleeding, surgical invasion or a septic condition are also related to D-dimer elevation, even though they didn't have VTE. Actually, 5 cases in VTE negative group showed very high D-dimer levels (> 10 μ g/mL), all of them were underwent emergent TC for bleeding or perforation with severe bowel inflammation. Therefore, D-dimer elevation isn't strong predictor of VTE, but we can use easily to suspect the thrombus. It's may be more useful for patients undergoing TPC or proctectomy whose preoperative condition is relatively stable.

This study had several limitations. First, the study was designed retrospectively at a single institution. Variables that could be collected from the database were limited. Pharmacological prophylaxis was not administered to all patients, and the administration period was not defined. CT examination was conducted in all patients preoperatively but not in all patients following surgery, and not exam the lower limb venous thrombus. Data of lower limb examination using ultrasound imaging were not collected. Lastly, the percentage of postoperative VTE prophylaxis with anticoagulant was only 31.4% in this study. This is too small in spite of that the risks of VTE in patients with UC has well known. Guideline states that strict administration of postoperative pharmacological prophylaxis was necessary, except the case having the risk of bleeding from remnant rectum [1].

Conclusion

We detected more postoperative VTE in our retrospective dataset than previous data. Especially, quarter cases of TPC + IPAA showed PMVT. Most cases were asymptomatic VTE but had the potential to be symptomatic with growth. It's important to recognize this result, and conduct the strict anticoagulant therapy.

Abbreviations

VTE: venous thromboembolism, TPC: total proctocolectomy, IPAA: ileal pouch-anal anastomosis, UC: ulcerative colitis, IBD; inflammatory bowel disease, CT: computed tomography, TC: total colectomy, PE: pulmonary embolism, DVT: deep vein thrombosis, PMVT: portal-mesenteric venous thrombosis, IQR: interquartile range,

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki. This study was approved by the Hiroshima University institutional review board (E-1636). The need of informed consent is waived by Hiroshima University hospital IRB. All participants received information about the conduct of the research, including the purpose of the study, and were given the opportunity to decline participation in the study. Because the opt-out method can be used without informed consent from the patient who had finished the surgery, it was published on the web.

Consent for publications

Not applicable

Availability of data and materials

The database used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they are no competing interests.

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This study has never funded by any foundation, company, or external source.

Author's Contributions.

NShima, NShige, and HO made the concept of this study. NShima, and YW design this study. HK, KY, and NShima collected data. ST, KU analyzed data and interpreted. Manuscript was prepared by NShima and SU, and edited by HO and ST. All authors read and approved the final manuscript.

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Figures

Fig. 1

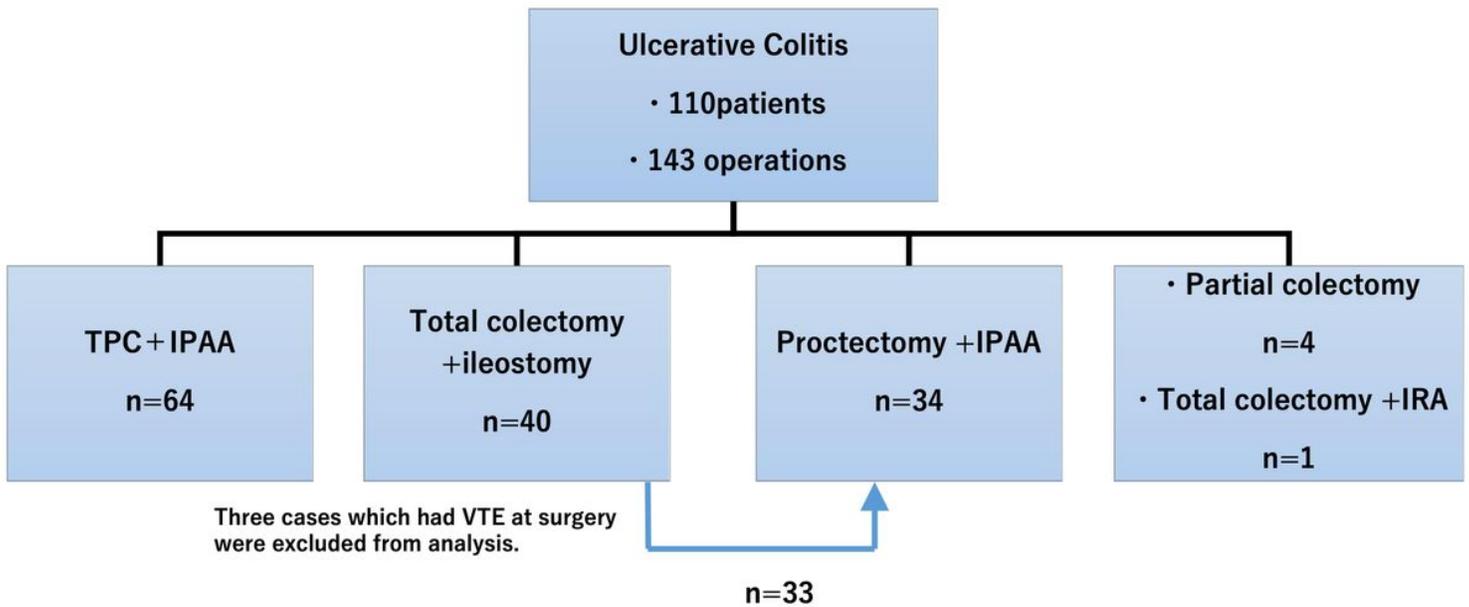
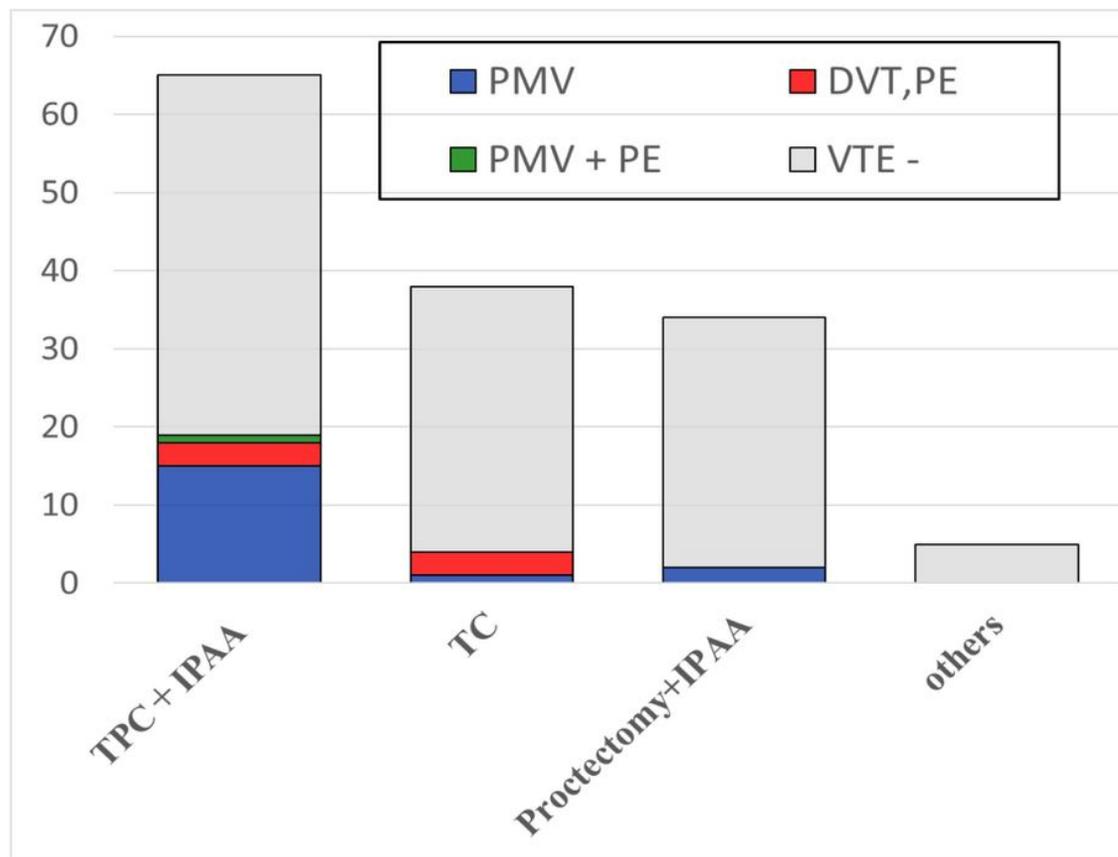


Figure 1

We enrolled a total 110 patients, including 143 operations. After total colectomy, 33 patients underwent proctocolectomy with IPAA. In total colectomy, 3 cases were excluded from the analysis because they had preoperative venous thromboembolism. IPAA, ileal pouch–anal anastomosis.

Fig. 2



	TPC+IPAA	TC	Proctectomy+IPAA
PMV	14	1	2
PE, DVT	3	3	0
PMV + PE	1	0	0

Figure 2

Correlation between surgical procedure and thrombosis site. PMVT frequently occurred after TPC with IPAA. PE and DVT occurred more frequently in patients who underwent TC with acute flare-ups of UC. DVT was included the central vein and femoral vein thrombus. TPC, total proctocolectomy; IPAA, ileal pouch–anal anastomosis; TC, total colectomy; PMV, portal–mesenteric venous thrombosis.