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Relationship between venous thromboembolism and inflammatory bowel disease in Taiwan: a nationwide retrospective cohort study

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Abstract

Background Inflammation significantly influences thrombosis development, with venous thromboembolism (VTE) risk linked to various systemic inflammatory diseases, but not fully established in inflammatory bowel disease (IBD). Using a population-based cohort study conducted in Taiwan, we investigated the impact of IBD on the risk of VTE, deep vein thrombosis (DVT), and pulmonary embolism (PE), as well as the impact of anti-IBD treatments.

Methods A study was conducted on a cohort of patients with IBD diagnosed between 2010 and 2019 using the National Health Insurance database. The risks of VTE, DVT, and PE, as well as anti-IBD treatment use, were examined using Cox proportional hazard regression analysis.

Results The overall number of person-years recorded for 12,126 patients with IBD (mean age: 49.18 years; 55.31% male) and 12,126 controls (mean age: 49.19 years; 55.31% male) was 64,057 and 72,056, with a follow-up duration for the two cohorts was 5.28 and 5.94 years, respectively. After adjusting for age, gender, and comorbidities, the adjusted hazard ratios (aHRs) of VTE, DVT, and PE in patients with IBD were 5.58 [95% confidence interval (CI) = 3.97–7.87], 5.48 (95% CI = 3.83–7.86), and 4.96 (95% CI = 2.00-12.35) times higher, respectively, than those in the control cohort. Male patients with IBD and those under the age of 50 were more likely to develop VTE (aHR = 8.54, 95% CI = 2.00-12.35; aHR = 15.75, 95% CI = 5.73–43.26, respectively). Compared to the cohort of patients with IBD receiving no treatment, patients receiving anti-IBD treatments did not show a significant change in the risk of developing VTE. Additionally, compared to the IV steroid cohort, patients with IBD who only used oral steroids had a substantially lower incidence of VTE, particularly with average doses of ≤ 80 mg (aHR = 0.24, 95% CI = 0.10–0.59).

Conclusion Patients with IBD are at an increased risk of developing VTE, particularly DVT and PE. While our study found that anti-IBD treatments did not significantly alter this risk, proactive management of associated factors

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and close monitoring remains essential for preventing VTE in this population. Identifying and addressing specific associated factors should be prioritized in clinical practice to mitigate the heightened risk of VTE in IBD patients.

Keywords Inflammatory bowel disease, Anti-IBD treatments, Venous thromboembolism, Cohort study, National health insurance database

Background

Inflammatory bowel disease (IBD) refers to a group of inflammatory conditions affecting the colon and small intestine. IBD, which causes chronic, recurrent diarrhea, and progressive inflammation that can damage the colonic mucosa, and entire gastrointestinal tract, is also known as Crohn's disease (CD) and ulcerative colitis (UC) [1]. Between 2001 and 2015, Taiwan saw an increase in CD and UC cases from 0.17 to 0.47 and from 0.54 to 0.95 new cases per 100,000 individuals, respectively [2]. IBD is becoming more common, with over 3 million Americans affected and an estimated 70,000 new cases diagnosed annually [3]. Specifically, the number of reported cases has stabilized in industrialized nations in Europe and North America, while it is rising in the Middle East and Asian countries [4].

In patients with IBD, the disease may result from inflammation, stricture, or penetration and fistulization. The accompanying problems may also result in a low quality of life and negative emotional consequences. IBD symptoms include abdominal pain and cramping, the passing of pus or mucus, and bloody diarrhea. IBD can impair both the musculoskeletal and dermatological systems [1]. Additional symptoms have been found in the ocular, renal, pulmonary, and hepatobiliary systems [5]. Patients with IBD may develop thromboembolic complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE), both of which are classified as venous thromboembolism (VTE), but these are frequently overlooked [6]. Bargen and Barker [7], who reported 18 cases of VTE among over 1000 patients treated for IBD at the Mayo Clinic, first recognized a relationship between IBD and VTE [7]. Since then, recent studies reveal that patients with IBD are a significantly higher risk of developing VTE, with over seven-fold greater risk reported [1]. Although there is substantial agreement that VTE and IBD are linked, the molecular pathophysiology of VTE in IBD remains unclear. However, over the last ten years, a growing body of research has been published outlining the factors that may influence this risk, including genetics, age, hospitalization history, disease activity, complicated IBD (fistula, stenosis, and abscess), pregnancy, drugs (corticosteroid use), and surgery [8].

Blood clots in one or more deep veins can cause DVT, increasing the likelihood of the clot breaking free, entering the circulation, and lodging in the lungs. PE is a potentially fatal condition caused by an embolic or thrombotic blockage of the pulmonary arterial system. Combined DVT and PE create VTE, a catastrophic illness with a 30-day case fatality rate of 11–30% [9]. According to 13 major cohort studies, the yearly prevalence rate of VTE in participants with IBD ranges between 0.55% and 6.15%, with an annual incidence rate of 0.15–1.9%. Extensive research conducted in several countries has consistently demonstrated that individuals with IBD are 1.7–5.9 times more likely to have VTE than non-IBD patients. Within some topic groupings, the danger may increase by 15 times. In a UK-based cohort of 13,756 patients with IBD, at-risk circumstances were explicitly linked to disease activity, with the hazard ratio (HR) for VTE events increasing from 2.1 to 8.4 during a flare and to 6.5 in those with chronic activity [10]. In general, the pathogenic specificity of the VTE risk may be higher for IBD than for chronic inflammation. In a retrospective study, those with IBD had a significantly higher risk of prior VTE compared to controls (OR, 3.6; 95% CI, 1.7–7.8); however, there were no differences in VTE rates between the control group and those with celiac disease or rheumatoid arthritis [11]. Notably, the prognosis for patients with VTE and IBD appears to be worse than that in the general population. VTE, along with gastrointestinal malignancy, sepsis, and respiratory diseases, is a leading cause of morbidity and death in individuals with IBD [10].

The five main classes of medications used in the treatment of IBD are aminosalicylates (5-aminosalicylic acid-based compounds), corticosteroids, immunomodulators (azathioprine, mercaptopurines, methotrexate, and cyclosporine), biologics (infliximab, adalimumab, and certolizumab), and small molecule drugs. Corticosteroids have three major adverse effects on the cardiovascular system: thromboembolism, dyslipidemia, and hypertension, all of which increase the risk of acute coronary syndrome and hasten the onset of atherosclerosis [12].

Chronic inflammation associated with IBD may increase the risk of PE, DVT, and ultimately, VTE. Few epidemiological studies have examined the link between IBD and VTE onset, particularly in Asian patients with IBD. Using a long-term national cohort study, we investigated whether IBD affects the incidence of VTE and the use of anti-IBD treatments in Taiwan. We also discuss a few factors that contribute to the increased risk of VTE for patients with IBD and on IBD treatments. This is an important topic because new evidence on the potential link between IBD, anti-IBD treatments, and VTE could

assist in raising awareness of this issue and providing guidelines for improving the health of patients with IBD.

Materials and methods

Data source

The Taiwan National Health Insurance Research Database (NHIRD), founded in 1995, covers 99.9% of the Taiwanese population. It contains a wide range of data, including patient demographics, medical history, and medication codes, for comprehensive analysis. Disease diagnoses were made using the International Classification of Diseases, Ninth Clinical Modification (ICD-9-CM) and the Tenth Revision, Clinical Modification (ICD-10-CM) to ensure a standardized and accurate classification. This meticulous approach enables robust analyses of health trends, medication patterns, and epidemiological research to inform evidence-based healthcare decisions. The NHIRD's inclusivity aids in investigating healthcare disparities among demographic groups. The Research Ethics Committee of China Medical University Hospital approved this study (CMUH111-REC2-109-CR-1).

Study population

In this population-based cohort study, individuals diagnosed with IBD (ICD-9-CM: 555 and 556; ICD-10-CM: K50 and K51) who had at least one hospital admission between 2010 and 2019 were assigned to the IBD cohort. The index date for the IBD cohort was defined as the date of the initial IBD diagnosis, whereas for the non-IBD cohort, it was chosen at random during the study period. We excluded subjects with a history of VTE, those without age and sex information, those with isolated pulmonary embolism (IPE; ICD-9-CM: 415.11; ICD-10-CM: I26.9, T80.0XXA, T81.718 A, T81.72XA, T82.817 A, and T82.818 A), those with exclusive outpatient records indicating IBD, and subjects in the control group undergoing treatment for IBD, before the index date. The non-IBD cohorts were frequency-matched in a 1:1 ratio based on age (5-year intervals), gender, and index year, as illustrated in Fig. 1.

Main outcome and relevant variables

The primary outcome of this study was the occurrence of VTE (ICD-9-CM: 415.1 and 451–453; ICD-10-CM: I26.9, I27.82, I80–I82, T80.0XXA, T81.718 A, T81.72XA, T82.817 A, and T82.818 A). VTE was further classified as DVT and PE. Patients with VTE were defined as those having at least two claims for outpatient care or one hospitalization visit to ensure the validity of the diagnosis. The end date of the follow-up period was the occurrence of VTE, death, or December 31, 2020, whichever occurred first. Comorbidities considered in the analysis included hyperlipidemia (ICD-9-CM: 272; ICD-10-CM: E71.30, E75.21, E75.22, E75.24, E75.3, E75.5, E75.6, E77, E78.0–E78.6, E78.70, E78.79, E78.8, and E78.9), obesity (ICD-9-CM: 278 and 783.1; ICD-10-CM: E66.09, E66.1, E66.8, E66.9, E66.01, E66.2, E65, E67.0, E67.1–E67.3, E67.8, E68, and R63.5), coronary artery disease (CAD; ICD-9-CM: 410–414; ICD-10-CM: I20–I25), hypertension (ICD-9-CM: 401–405; ICD-10-CM: I10–I13, I15, and N26.2), and chronic kidney disease (CKD; ICD-9-CM: 585 and 586; ICD-10-CM: N18 and N19). We also investigated the effect of IBD treatment on the risk

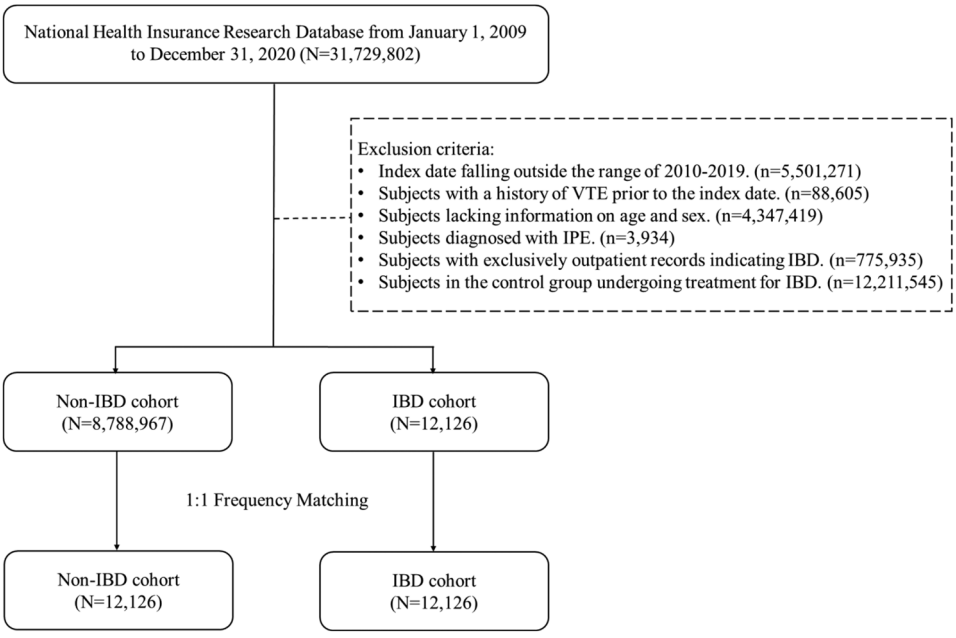

Fig. 1 Flow chart

of developing VTE. Aminosalicylates, corticosteroids, immunomodulators, biologics, and small molecules drugs are among the medications used to treat IBD, in addition to surgical interventions. We conducted a sensitivity analysis following with Cox model by setting the minimum treatment duration to 28 days. This approach excluded data from individuals who had a history of treatment prior to the study but did not receive treatment during the study period, as well as patients whose prior treatment duration was less than 28 days. The term "average dose of steroids" refers to the mean daily dose administered over a specific treatment period. This is calculated by summing the total dose of steroids given during the treatment period and dividing it by the number of days the patient received the medication.

Statistical analysis

To compare the population distributions of the IBD and non-IBD cohorts, we calculated the frequencies and percentages of categorical variables, as well as the means and standard deviations (SD) of continuous variables in both cohorts. The chi-square test for categorical variables and the Student's t-test for continuous variables were used to compare the IBD and non-IBD cohorts.

To analyze survival data, unadjusted hazard ratios (HRs) (crude HRs, cHRs) and multivariable-adjusted HRs (aHRs) with corresponding 95% confidence intervals (CIs) for VTE risk between the two cohorts were analyzed using the Cox proportional hazard regression model. The aHR was obtained from a multivariate model including sex, age, and comorbidities. We measured the cumulative incidence curves between patients with PUD and comparison cohorts using the Kaplan–Meier method and tested the differences using the log-rank test by adjusted with the variables. Except for the construction of the cumulative incidence curve, which used R software version 4.3.1 (R Software Inc., San Francisco, CA, USA), all other statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, UCA). The statistical significance level was set at $p < 0.05$.

Results

Table 1 shows the baseline characteristics of the study population, which included 12,126 patients with IBD and an equal number of patients without IBD after frequency matching. There were no significant differences in sex or age following matching ($p > 0.05$). Male patients accounted for 55.31% of the study population. The mean age of the two cohorts was 49.18 (SD = 23.94) and 49.19 (SD = 23.96), respectively. The most common comorbidities observed in patients with IBD such as hyperlipidemia, obesity, CAD, hypertension, and

Table 1 Demographic characteristics, comorbidity, and medication in patient with and without IBD

Variable	IBD				*p*-value
	No *N* = 12,126		Yes *N* = 12,126		
	N	(%)	*N*	(%)	
Sex					> 0.999
Female	5419	(44.69)	5419	(44.69)	
Male	6707	(55.31)	6707	(55.31)	
Age					> 0.999
≤ 49	5732	(47.27)	5732	(47.27)	
50–64	2788	(22.99)	2788	(22.99)	
≥ 65	3606	(29.74)	3606	(29.74)	
mean (SD)[a]	49.19	(23.96)	49.18	(23.94)	0.966
Comorbidity					
Hyperlipidemia	1420	(11.71)	3130	(25.81)	< 0.001
Obesity	45	(0.37)	90	(0.74)	< 0.001
Coronary artery disease (CAD)	537	(4.43)	2053	(16.93)	< 0.001
Hypertension	1805	(14.89)	4494	(37.06)	< 0.001
Chronic kidney disease (CKD)	125	(1.03)	991	(8.17)	< 0.001
Medication					
Corticosteroids			10,454	(86.21)	
Immunomodulators			1862	(15.36)	
Aminosalicylates			5845	(48.20)	
Biologics and small molecule			1009	(8.32)	
Surgical treatment			2286	(18.85)	
Follow-up time, years					
mean (SD)[a]	5.94	(2.95)	5.28	(3.17)	< 0.001

[a]Student's t-test; Chi-square test; SD: standard deviation

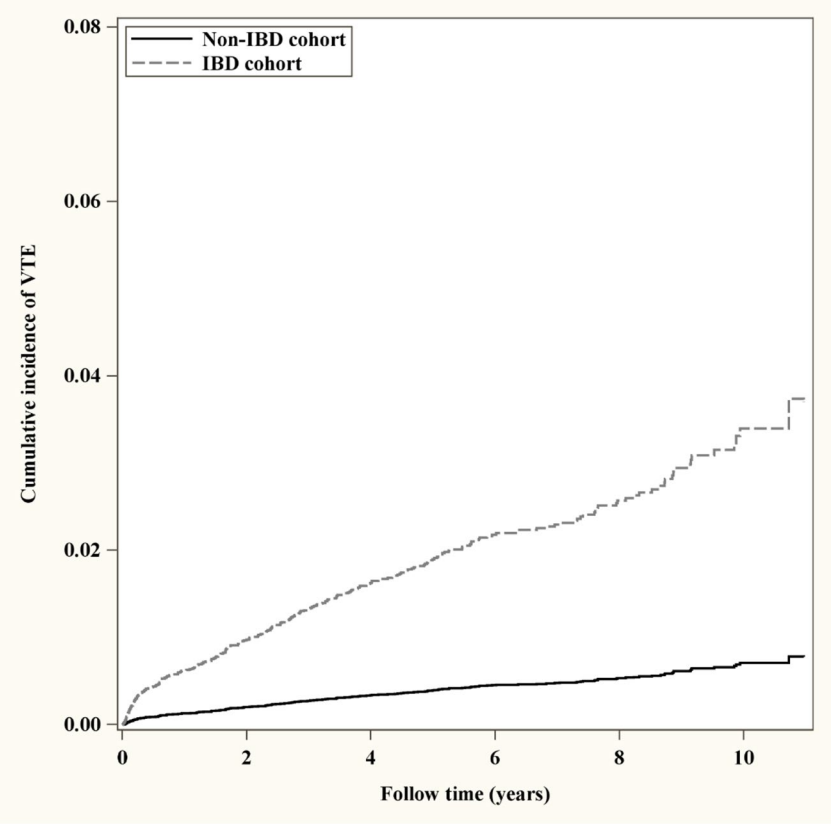

Fig. 2 Cumulative incidence of VTE compared between the cohort with and without IBD using the Kaplan–Meier method

Table 2 Comparison of incidence and hazard ratio of VTE stratified by sex, age, and comorbidity between with and without IBD

Variable	IBD						cHR	(95% CI)	aHR	(95% CI)
	No			Yes						
	n	PY	IR	*n*	PY	IR				
All	42	72056.34	0.58	249	64057.11	3.89	6.54	(4.71, 9.06)***	5.58	(3.97, 7.87)***
Sex										
Female	27	31973.34	0.84	119	28774.35	4.14	4.81	(3.17, 7.31)***	3.95	(2.53, 6.16)***
Male	15	40083.00	0.37	130	35282.76	3.68	9.63	(5.64, 16.44)***	8.54	(4.92, 14.82)***
Age										
≤ 49	4	36658.52	0.11	70	35741.89	1.96	17.92	(6.55, 49.07)***	15.75	(5.73, 43.26)***
50–64	12	16209.80	0.74	67	14493.62	4.62	6.12	(3.31, 11.31)***	6.11	(3.27, 11.44)***
≥ 65	26	19188.02	1.36	112	13821.60	8.10	5.67	(3.69, 8.69)***	3.45	(2.11, 5.64)***
Comorbidity										
No	13	60631.79	0.21	96	40224.83	2.39	11.12	(6.23, 19.85)***	15.8	(8.69, 28.75)***
Yes	29	11424.55	2.54	153	23832.28	6.42	2.49	(1.68, 3.71)***	2.39	(1.60, 3.55)***

PY: person-year; IR: incidence rate, per 1000 person-years; cHR: crude hazard ratio; CI: confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; aHR: adjusted hazard ratio, adjusted for age, sex, and comorbidities of hyperlipidemia, obesity, CAD, hypertension, and CKD

CKD were included. Patients with IBD had significantly higher rates of comorbidities compared to the control group. Among the patients with IBD, 86.21% used corticosteroids, 48.20% used aminosalicylates, 15.36% used immunomodulators, 8.32% used biologics and small molecules, and 18.85% underwent IBD surgery. The mean follow-up time for the two cohorts was 5.28 (SD = 3.17) and 5.94 (SD = 2.95) years, respectively. Figure 2 shows a considerably greater cumulative incidence curve of VTE for patients with IBD compared to patients without IBD after adjusted with the variables including sex, age, and comorbidities ($p < 0.001$). Table 2 compares the overall and stratified risk analysis of VTE between the IBD and non-IBD cohorts based on sex, age, and comorbidities. After adjusting for sex, age, and comorbidities, the IBD cohort had a 5.58-fold higher incidence of VTE (95%

Table 3 Cox model measured hazard ratio and 95% confidence intervals of VTE associated with corticosteroids

Variable	VTE			cHR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)
	n	PY	IR						
Non-IBD controls (*N* = 12126)	42	72,056	0.58	1.00	(reference)	1.00	(reference)		
IBD without anti-IBD treatment (*N* = 1135)	22	6151	3.58	6.03	(3.60, 10.09)***	4.93	(2.90, 8.38)***	1.00	(Reference)
IBD with anti-IBD treatment (*N* = 6840)	156	37,890	4.12	7.00 (4.98, 9.84)***		6.04 (4.20, 8.69)***		0.97 (0.62, 1.51)	
Corticosteroids (*N* = 6087)	133	34,572	3.85	6.58	(4.65, 9.30)***	5.68	(3.92, 8.23)***	0.90	(0.57, 1.42)
IV steroids (*N* = 3687)	90	19,792	4.55	7.72	(5.35, 11.14)***	6.48	(4.37, 9.62)***	1.12	(0.70, 1.79)
Oral steroids (*N* = 5558)	121	32,026	3.78	6.47	(4.55, 9.18)***	5.69	(3.91, 8.28)***	0.93	(0.59, 1.47)
Other steroids (*N* = 1940)	39	13,066	2.98	5.21	(3.36, 8.06)***	3.62	(2.26, 5.79)***	0.70	(0.41, 1.20)
Immunomodulators (*N* = 1827)	38	10,442	3.64	6.24	(4.03, 9.69)***	6.86	(4.29, 10.98)***	1.17	(0.69, 1.99)
Aminosalicylates (*N* = 5409)	126	29,785	4.23	7.18	(5.06, 10.18)***	6.52	(4.49, 9.48)***	1.02	(0.65, 1.61)
Biologics and small molecule (*N* = 1031)	10	6094	1.64	2.82	(1.41, 5.62)**	3.99	(1.94, 8.20)***	0.59	(0.27, 1.26)
IBD without surgical treatment (*N* = 6636)	155	36,954	4.19	7.13	(5.07, 10.02)***	5.96	(4.15, 8.55)***	1.00	(Reference)
Surgical treatment (*N* = 1339)	23	7087	3.25	5.49	(3.30, 9.12)***	3.74	(2.18, 6.41)***	0.74	(0.48, 1.15)

PY: person-year; IR: incidence rate, per 1000 person-years; cHR: crude hazard ratio; CI: confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ aHR: adjusted hazard ratio, adjusted for age, sex, and comorbidities of hyperlipidemia, obesity, CAD, hypertension, and CKD

Table 4 Cox model measured hazard ratio and 95% confidence intervals of VTE and PE associated IBD in patients

Variable	VTE			cHR	(95% CI)	aHR	(95% CI)
	n	PY	IR				
Only use IV steroids (*N* = 466)	15	1677.58	8.94	1	(reference)	1	(reference)
Only use oral steroids							
Average does ≤ 20 mg (*N* = 1108)	9	7766.63	1.16	0.14	(0.06, 0.32)***	0.27	(0.12, 0.64)**
Average does ≤ 80 mg (*N* = 988)	7	5512.13	1.27	0.15	(0.06, 0.37)***	0.24	(0.10, 0.59)**
Average does > 80 mg (*N* = 1075)	25	4716.02	5.30	0.61	(0.32, 1.15)	0.95	(0.49, 1.82)
Only use other steroids (*N* = 431)	6	2449.23	2.45	0.29	(0.11, 0.76)*	0.35	(0.13, 0.89)*

PY: person-year; IR: incidence rate, per 1000 person-years; cHR: crude hazard ratio; CI: confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; aHR: adjusted hazard ratio, adjusted for age, sex, and comorbidities of hyperlipidemia, obesity, CAD, hypertension, and CKD

Table 5 Cox model measured hazard ratio and 95% confidence intervals of DVT and PE associated IBD in patients

Outcome	IBD						cHR	(95% CI)	aHR	(95% CI)
	No			Yes						
	n	PY	IR	*n*	PY	IR				
DVT	38	72062.35	0.53	222	64099.44	3.46	6.45	(4.57, 9.10)***	5.48	(3.83, 7.86)***
PE	6	72186.59	0.08	36	64703.29	0.56	6.53	(2.75, 15.49)***	4.96	(2.00, 12.35)***

PY: person-year; IR: incidence rate, per 1000 person-years; cHR: crude hazard ratio; CI: confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; aHR: adjusted hazard ratio, adjusted for age, sex, and comorbidities of hyperlipidemia, obesity, CAD, hypertension, and CKD

CI = 3.97–7.87). When stratified by gender, females in the IBD cohort had a 3.95-fold greater risk of VTE compared to the control cohort (95% CI = 2.53–6.16), whereas males in the IBD cohort had an 8.54-fold higher risk (95% CI = 4.92–14.82). Patients with IBD aged ≤ 49 years had a 15.75-fold higher incidence of VTE compared to the non-IBD cohort (95% CI = 5.73–43.26). In the IBD cohort, those aged 50–64 years had a 6.11-fold greater risk of VTE (95% CI = 3.27–11.44), whereas those aged ≥ 65 years had a 3.45-fold increased risk of VTE (95% CI = 2.11–5.64). Moreover, among patients without comorbidities, the IBD cohort had a 15.8-fold higher incidence of VTE than the non-IBD cohort (95% CI = 8.69–28.75). However, patients with comorbidities in the IBD cohort had a 2.39-fold higher risk of VTE than those in the non-IBD cohort (95% CI = 1.60–3.55).

Table 3 shows the incidence, crude hazard ratios, and adjusted HR of VTE associated with IBD treatment. Individuals with IBD had a higher risk of VTE than those without IBD, even if they received treatment. When compared to patients with IBD who did not receive treatment, there was no significant difference in VTE risk among those receiving different treatment regimens. Table 4 presents the risk of VTE in patients with IBD treated with various corticosteroids. Patients with IBD who took oral steroids at doses of ≤ 20 mg to ≤ 80 mg had a lower risk of VTE compared to those who only received intravenous (IV) steroids. Similarly, patients with IBD treated solely with other steroids had a lower VTE risk than those treated only with IV steroids. Table 5 illustrates the risks of DVT and PE. After adjusting for sex, age, and comorbidities, individuals with IBD had a 5.48-fold greater risk

of DVT than those without IBD (95% CI = 3.83–7.86). Furthermore, the risk of PE in patients with IBD was 4.96 times higher than that in patients without IBD (95% CI = 2.00–12.35).

Discussion

For the first time, an epidemiological approach is being used to determine whether patients with IBD in an Asian population have an increased risk of developing VTE, DVT, and PE, as well as the impact of anti-IBD treatments. The nationwide population-based cohort study found that, after adjusting for age, gender, and comorbidities, patients with IBD had a 6.54-fold (aHR = 5.58, 95% CI = 3.97–7.87), 6.45-fold (aHR = 5.48, 95% CI = 3.83–7.86), and 6.53-fold (aHR = 4.96, 95% CI = 2.00–12.35) higher risk of developing VTE, DVT, and PE, respectively, compared to non-IBD controls. Furthermore, our findings revealed that among patients with IBD in Taiwan, the incidence of VTE was 3.89 per 1000 person-years, 3.46 per 1000 person-years for DVT, and 0.56 per 1000 person-years for PE. While the incidence of VTE does increase with age, the relative risk is inversely related to age in other at-risk categories, such as participants with IBD under 49 years old, where the risk is between 5.73 and 43.26 times higher than for the controls. This is consistent with previous findings.[10] Males had higher VTE rates than females. Patients with IBD without comorbidities showed a 15.8-fold higher aHR for VTE than matched controls. In patients with IBD without treatment, the aHR risk of VTE was 4.93 (95% CI = 2.90–8.38) as compared to non-IBD controls. The surgical setting was also evaluated and showed no significant impact on VTE risk in patients with IBD. Even after controlling for potential variables, patients with IBD had an independent risk of developing VTE, DVT, and PE, despite having a significantly greater comorbidity rate than that in the non-IBD controls. However, patients with IBD treated with oral steroids had a considerably lower risk of developing VTE than those patients with IBD receiving IV steroid treatment. However, this finding should be viewed with caution because IV corticosteroid treatment, often used in patients with active and severe IBD, may itself elevate the risk of developing VTE. Therefore, patients with severe IBD, particularly those experiencing active disease or frequent relapses, are at an inherently higher risk of VTE.

The evidence from the literature suggests that thrombosis is a distinguishing feature of IBD that influences both the pathophysiology of the disease and the frequency of thromboembolic events. Virchow's triad identifies three factors that increase the risk of thrombosis: hypercoagulability, endothelial dysfunction, and venous stasis [12]. VTE is more prevalent in patients with IBD, increasing morbidity and mortality [12, 13]. IBD has a major impact on the coagulation cascade, resulting in abnormalities such as elevated fibrin, platelet counts, and coagulation factors V and VIII. Activated circulating platelets and platelet aggregates are more prevalent in patients with IBD and may increase the risk of thrombosis [13]. IBD causes both systemic and localized inflammation which activates coagulation cascades. Proinflammatory cytokines, such as IL-6, increase coagulation without causing concurrent fibrinolysis. Patients with IBD have reduced fibrinolysis, as demonstrated by elevated plasminogen activator inhibitor (PAI) levels and lower plasma tissue plasminogen activator (tPA) activity. Other risk factors include surgery, prolonged immobilization, central venous catheters, fluid depletion, genetic risk factors, steroid therapy, oral contraceptives, high antiphospholipid antibody levels, and hyperhomocysteinemia caused by vitamin deficiencies [1]. Patients with IBD frequently have multiple risk factors. While no risk factors are more important than others, it is clear that a patient's risk of thrombosis increases as the number of risk factors increase.

It has been postulated that in IBD, the coagulation cascade is more active, implying a strong correlation between disease activity and VTE risk [1]. Grainge et al. [14] conducted the only population-based study in the United Kingdom to investigate the association between IBD activity and VTE incidence. When they compared patients with IBD's acute disease flares to their remission times, they identified a 4.5-fold higher incidence of VTE. Because the need for corticosteroids is a defining feature of an IBD flare, the Grainge study included patients with moderate-to-severe flares. In that study, corticosteroid medication may have raised the likelihood of developing VTE. This is consistent with our findings, which showed that patients with IBD who used IV steroids had a higher incidence of VTE than those who used oral steroids. We found that patients treated with oral corticosteroids at doses of ≤ 80 mg had a lower risk of VTE compared to those receiving IV corticosteroids. However, we recognize that this may reflect differences in disease severity rather than the effect of the treatment itself. Patients requiring IV corticosteroids likely have more severe disease, which increases their baseline VTE risk. Disease severity, particularly the need for hospitalization, is an important factor that may confound the association between corticosteroid treatment and VTE risk [8, 14]. Unfortunately, due to limitations in our dataset, we could not fully adjust for disease severity as a confounding factor. Additionally, regarding the analysis of hospitalization duration in relation to different treatment regimens, we acknowledge that this is an important consideration. Unfortunately, we lacked sufficient power to robustly analyze hospitalization duration against the various treatment regimens. Furthermore, D'Ascenzo et

al. [11] demonstrated that VTE is more uniquely associated with IBD when compared to celiac disease and rheumatoid arthritis (RA), while arterial thromboembolism is increased in both IBD and RA. Thus, the underlying processes that contribute to the pathophysiology of IBD might be local and systemic intravascular hypercoagulable and prothrombotic states, as well as frank thrombosis.

In a 2018 meta-analysis by Sarlos et al., corticosteroid use was linked to an increased incidence of VTE episodes among patients with IBD (OR: 2.2; 95% CI: 1.7–2.9) [15]. Corticosteroids are an important treatment option for IBD; however, they can increase the incidence of VTE in patients who have not had colorectal surgery [15, 16]. This could be attributed to the activation of the PAI-1 gene in cells, which increases PAI-1 levels while decreasing tPA levels, resulting in hypercoagulability [17]. Furthermore, the use of corticosteroids may suggest a more advanced stage of illness, as they are required to treat severe cases and achieve remission [14]. Some researchers suggest that disease activity increases the risk of VTE, whereas others believe that patients with corticosteroid-treated IBD are more likely to experience illness flares, increasing the risk of VTE [18]. Corticosteroids alone have been shown to increase the incidence of VTE, regardless of the inflammatory conditions [19]. They are associated with a higher incidence of VTE, particularly in the first 30 days, as well as the highest doses for disease aggravation [20]. Our findings showed that the disease was more active in patients with IBD receiving IV steroid therapies, while oral steroid medication was associated with a significantly lower risk of developing VTE. Thus, our study found that the severity of the illness was related to the likelihood of VTE. The risk of thrombosis or aggravation of inflammatory conditions is unclear, and whether corticosteroids improve coagulation is controversial.

Prednisolone treatment in vitro increased thrombin production, indicating a procoagulant state. This indicates that coagulation is induced by an interaction with a procoagulant trigger, such as a disease [21]. Prednisolone also increased von Willebrand factor (vWF) and PAI-1, which contribute to platelet adhesion and bind to factor VIII. In the absence of other inflammatory agents, corticosteroids appear to activate leukocytes and endothelial cells, increasing vWF gene transcription but not vWF secretion [21]. The increase in several coagulation factors, activation of PAI-1, and improved vWF gene expression could explain the shift in hemostatic balance to a procoagulant state.

Because 5-ASA, a commonly used IBD treatment, has anti-inflammatory and antiplatelet properties, it may help patients avoid VTE episodes [22]. TNFα blockers have potent anti-inflammatory effects; however, there is no evidence that they reduce the risk of VTE in patients with IBD. Although patients with IBD have higher TNFα levels, anti-TNFα agents are not contraindicated in IBD; rather, they are widely used as an effective treatment for moderate to severe IBD. These biologics help reduce inflammation and maintain remission in patients who do not respond adequately to conventional therapies. However, their use must be carefully considered in patients with specific comorbidities, such as active infections or a history of malignancy, where the risk-benefit balance needs to be evaluated. In both experimental and clinical trials, almost every medication used to treat IBD has been associated with hemostatic system anomalies. Both hypo- and hypercoagulating corticosteroids have been linked to blood coagulation abnormalities [22]. Studies using 5-ASA to treat platelets from patients with IBD have yielded inconsistent results. In vitro, 5-ASA substantially reduces both thrombin-induced and spontaneous platelet activation [23]. Platelets from patients with IBD treated with 5-ASA showed lower expression levels of P-selectin, a surface marker for platelet activation, and lower plasma levels of Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES), a prothrombotic platelet cytokine [23]. In contrast, platelet aggregation and fibrinolysis were unchanged in a trial of six patients with IBD treated with 5-ASA [24].

Patients with IBD who used thiopurines reported fewer platelet leukocyte aggregates than those who did not [25]. The in vitro studies showed that 6-mercaptopurine and azathioprine had antithrombotic effects. Methotrexate, a folate antagonist, is known to increase hyperhomocysteinemia and is linked to the risk of thrombosis when given to patients with IBD [26]. Cyclosporine has been associated with thrombogenicity both in vitro and in vivo. In vitro studies with cyclosporine revealed increased platelet aggregation and endothelial cell activation. A decrease in PAI-1 activity has also been linked to impaired cyclosporine-induced fibrinolysis [27]. These studies demonstrating thrombotic events in patients treated with cyclosporine have corroborated the in vitro thrombogenicity of the drug in vivo.

In contrast, immunosuppressive drugs such as anti-TNFα biologics are thought to reduce the risk of VTE. Yoshida et al. [28] discovered that TNFα was critical in the hypercoagulable condition in animal models of colitis. Since then, the idea that inhibiting TNFα may reduce the frequency of VTE in patients with IBD has emerged. In a single-center retrospective analysis, taking anti-TNFα drugs was linked to a lower risk of VTE (OR: 0.2; 95% CI: 0.04–0.99), but using corticosteroids increased the risk of VTE fourfold [29]. Using a national insurance database for the United States, Higgins et al. [19] revealed that patients on biologics had an approximately five-fold lower incidence of VTE events than those on corticosteroids. This has already been established in numerous

trials with anti-TNFα drugs; however, additional research is needed to evaluate more recently discovered biologics. Our findings revealed that monoclonal antibody treatment reduced the risk of VTE in patients with IBD by 0.54-fold when compared to patients with IBD but without treatment, although the result was not statistically significant.

Patients with IBD are likely to develop VTE in early infancy, and those aged 20 and younger exhibited a VTE HR that was more than six times higher than that of age- and sex-matched patients without IBD [30]. Younger patients with IBD had a nearly four-fold higher relative risk of a VTE event than older patients with IBD (≥ 60 years old), but the annual incidence of events was significantly lower in the younger IBD patient population (8.9/10000 person-years vs. 54.6/10000 person-years, respectively) [30]. This is consistent with our findings: whereas the incidence of VTE rises with age, other at-risk groups, such as patients with IBD under the age of 49, have a lower relative risk; in these groups, the risk is 5.73–43.26 times higher than in controls.

Given the rarity of VTE and the multiple side effects associated with IBD treatment, clinicians should try to rule out the likelihood of side effects from specific medications used to treat IBD before assuming disease activity is a causal factor in patients presenting with VTE. These symptoms may be caused by acute or chronic inflammation, pharmacological toxicity, or genetic predisposition. Early identification lowers the impact of the disease's natural progression and helps to avert complications. Some of the most crucial primary preventive interventions for VTE include managing conventional and non-traditional VTE risk factors, maintaining remission for as long as possible, conducting periodic VTE evaluations, and using anticoagulants.

Our findings are based on a countrywide population-based longitudinal research design assessing the risk of VTE, DVT, and PE in Asian patients. Every Taiwanese citizen is assigned a unique personal identification number, which allows researchers to trace research participants during the follow-up period using NHI data. Therefore, our results apply to the entire Taiwanese population.

When evaluating the findings, it is important to keep the study's limitations in mind. The comparison cohort had fewer hospitalized patients than the IBD cohort, which may have led to an overestimation of DVT and PE risks. VTE is more likely to develop later in hospitalized patients with autoimmune diseases [8]. However, because VTE is a common complication of hospitalization for severe medical diseases or surgery, our comparator sample included inpatients, which may have reduced the chance of overestimating the risk. The NHI auditing process can reduce diagnostic ambiguity and misclassification, even if healthcare claims data may have a bias in the major outcomes. The main findings of our study may have been influenced by the lack of pharmacological data for hormone replacement therapy, contraceptives, glucocorticosteroid therapies, and anticoagulants. Furthermore, there are no national guidelines for preventing VTE. Our nationwide population-based cohort study, which examined 12,126 patients with IBD over a follow-up period of approximately 64,057 person-years, concluded that compared to the general population, patients with IBD have a 5.58-, 5.48-, and 4.96-fold higher risk of developing VTE, DVT, and PE, respectively. These findings highlight the importance of a comprehensive strategy for addressing potential associated factors in VTE development. Further research is necessary on the biochemical underpinnings of IBD and how they affect VTE.

Several limitations of this study should be acknowledged. As these were observational studies, inherent biases exist in evaluating the association between IBD and VTE. While the correlation between IBD and VTE might be strengthened when considering factors such as smoking or BMI, we were unable to analyze additional potential confounders, including nutrition, alcohol use, physical activity, genetic predispositions, family history, IBD disease severity, and other coexisting medical conditions, including the presence or absence of extra-intestinal complications. Patients with more severe IBD, particularly those requiring IV steroid treatment, are at an inherently higher risk of VTE. These unmeasured variables could influence the observed association and may introduce residual confounding. Another limitation arises from the nature of observational studies, where causality cannot be definitively established. Although we identified a correlation between IBD and an increased risk of VTE, this does not confirm a direct causal link. Moreover, because VTE is notoriously difficult to diagnose, a significant risk of misclassification exists. Many cases of VTE are asymptomatic, and in some instances, a sudden fatal PE may be the first and only manifestation of the condition. This issue is compounded by the fact that only about 20% of PE are diagnosed with objective testing despite minor improvements in ante-mortem diagnostic rates over time [1]. Additionally, reliance on administrative databases or medical records for VTE diagnoses may lead to inaccuracies, as subclinical cases of VTE may go undetected. Cases of IBD and other diseases were identified based on physician-documented medical records rather than comprehensive clinical data. However, the diagnoses of IBD and VTE, DVT, and PE adhered to conventional symptomatic criteria, typical side effects, and imaging findings, which were reviewed by experts to ensure reliability. By accounting for comorbidities, the study aimed to minimize the confounding effects of

medications. Nonetheless, retrospective studies are subject to inherent biases, such as categorization bias, which may impact statistical reliability. Despite these limitations, Taiwan's NHI program ensures high data accuracy through extensive coverage and rigorous claim reviews conducted by reimbursement professionals and peer reviewers [31]. Finally, observational studies are subject to selection bias, as the study populations may not fully represent the broader IBD population, particularly concerning disease severity, medication use, and healthcare access, all of which could affect VTE risk. Future studies account for disease severity when assessing the impact of different treatment regimens on VTE risk are needed.

Our findings have significant clinical and public health implications. It is essential to consider whether the non-IBD group in our study accurately reflects the general population and to evaluate whether the incidence of thrombosis in this group aligns with reported rates in the general population. Thus, we performed an additional comparison after matching patients in a 1:10 ratio by index year, examining the baseline characteristics of individuals with and without IBD and evaluating the IBD-associated risk of VTE. The results were consistent with the trends observed in the original dataset (data not shown). We believe that this study, which found a higher incidence of VTE among patients with IBD, will contribute to greater public awareness of this issue. Based on this growing body of evidence, many practice guidelines now include recommendations on VTE risk in patients with IBD. It is crucial to note that most of the assessments were previously completed. A potential source of bias arises because most conventional medical records were not reviewed when comparing the IBD group with other patients or healthy controls.

Conclusion and relevance

Our findings suggest that IBD is associated with an increased risk of VTE, including DVT and PE, although the exact mechanisms underlying this elevated risk are not fully understood. While many studies have focused on inflammation and its systemic effects, further research is needed to uncover the specific processes involved. Current data does not clearly demonstrate that anti-IBD treatments reduce the risk of VTE. Additionally, younger individuals with IBD may be more likely to develop the disease earlier in life. Until more is known about the significance of specific associated factors, careful risk assessment and proactive management are essential. Prospective studies and clinical trials are needed to clarify the role of acute flare-ups and the use of medications in VTE development. Future trials should aim to resolve uncertainties regarding VTE prevention in patients with active disease, as well as the optimal duration of VTE prophylaxis following hospitalization.

Abbreviations

5-ASA	5-Aminosalicylates
aHRs	Adjusted hazard ratios
CAD	Coronary artery disease
CD	Crohn's disease
CI	Confidence interval
CKD	Chronic kidney disease
DVT	Deep vein thrombosis
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD-9/10-CM	International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification
IV	Iintravenous
LHID	Longitudinal Health Insurance Database
NHIRD	National Health Insurance Research Database
OR	Odd ratio
PAI	Plasminogen activator inhibitor
PE	Pulmonary embolism
RANTES	Regulated upon Activation Normal T-cell Expressed and Secreted
SD	Standard deviations
tPA	Tissue plasminogen activator
UC	Ulcerative colitis
VTE	Venous thromboembolism
vWF	Von Willebrand factor

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Author contributions

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Data availability

The published publication contains all of the data that were created or examined during this investigation. Although institutional restrictions prevent data sharing from being made publicly available, the China Medical University Hospital may provide authorization to share data upon request.

Declarations

Ethical approval and consent to participate

The NHIRD encrypts the patients' personal information to protect their privacy. It also provides researchers with anonymized identification numbers connected to key claim information such as sex, date of birth, medical services used, and prescriptions. Therefore, patient consent was not required to access NHIRD. To satisfy the criteria for exemption, the China Medical University Institutional Review Board (IRB) issued a clearance (CMUH111-REC2-109-CR-1). The IRB Review Board waived the requirement for permission.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Yuhara H, Steinmaus C, Corley D, et al. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;37:953–62.
2. Lin WC, Tai WC, Chang CH, et al. Real-world evidence of effectiveness and safety of Vedolizumab for inflammatory bowel disease in Taiwan: A prospective nationwide registry (VIOLET) study. Inflamm Bowel Dis. 2023;29:1730–40.
3. Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of inflammatory bowel disease among adults aged ≥ 18 years - United States, 2015. MMWR Morb Mortal Wkly Rep. 2016;65:1166–9.
4. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut. 2015;64:1063–71.
5. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2011;7:235–41.
6. Zitomersky NL, Verhave M, Trenor CC. Thrombosis and inflammatory bowel disease: a call for improved awareness and prevention. Inflamm Bowel Dis. 2011;17:458–70.
7. Bargen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. Arch Intern Med (Chic). 1936;58:17–31.
8. Cheng K, Faye AS. Venous thromboembolism in inflammatory bowel disease. World J Gastroenterol. 2020;26:1231–41.
9. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117:19–25.
10. Tan VP, Chung A, Yan BP, et al. Venous and arterial disease in inflammatory bowel disease. J Gastroenterol Hepatol. 2013;28:1095–113.
11. D'Ascenzo F, Bruno F, Iannaccone M, et al. Patients with inflammatory bowel disease are at increased risk of atherothrombotic disease: A systematic review with meta-analysis. Int J Cardiol. 2023;378:96–104.
12. Bunu DM, Timofte CE, Ciocoiu M, et al. Cardiovascular manifestations of inflammatory bowel disease: pathogenesis, diagnosis, and preventive strategies. Gastroenterol Res Pract. 2019;2019:3012509.
13. Murthy SK, Nguyen GC. Venous thromboembolism in inflammatory bowel disease: an epidemiological review. Am J Gastroenterol. 2011;106:713–8.
14. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet. 2010;375:657–63.
15. Sarlos P, Szemes K, Hegyi P, et al. Steroid but not biological therapy elevates the risk of venous thromboembolic events in inflammatory bowel disease: A meta-analysis. J Crohns Colitis. 2018;12:489–98.
16. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020;158:1450–61.
17. van Zaane B, Nur E, Squizzato A, et al. Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors. J Thromb Haemost. 2010;8:2483–93.
18. Dai C, Jiang M, Cao Q. Steroids and the risk of venous thromboembolic events in inflammatory bowel disease. J Crohns Colitis. 2018;12:627.
19. Higgins PD, Skup M, Mulani PM, et al. Increased risk of venous thromboembolic events with corticosteroid vs biologic therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2015;13:316–21.
20. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med. 2013;173:743–52.
21. Majoor CJ, Sneeboer MM, de Kievit A, et al. The influence of corticosteroids on hemostasis in healthy subjects. J Thromb Haemost. 2016;14:716–23.
22. Rungoe C, Basit S, Ranthe MF, et al. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut. 2013;62:689–94.
23. Carty E, MacEy M, Rampton DS. Inhibition of platelet activation by 5-aminosalicylic acid in inflammatory bowel disease. Aliment Pharmacol Ther. 2000;14:1169–79.
24. Winther K, Bondesen S, Hansen SH, et al. Lack of effect of 5-aminosalicylic acid on platelet aggregation and fibrinolytic activity in vivo and in vitro. Eur J Clin Pharmacol. 1987;33:419–22.
25. Irving PM, Macey MG, Shah U, et al. Formation of platelet-leukocyte aggregates in inflammatory bowel disease. Inflamm Bowel Dis. 2004;10:361–72.
26. Peyrin-Biroulet L, Rodriguez-Guéant RM, Chamaillard M, et al. Vascular and cellular stress in inflammatory bowel disease: revisiting the role of homocysteine. Am J Gastroenterol. 2007;102:1108–15.
27. van den Dorpel MA, Veld AJ, Levi M, et al. Beneficial effects of conversion from cyclosporine to azathioprine on fibrinolysis in renal transplant recipients. Arterioscler Thromb Vasc Biol. 1999;19:1555–8.
28. Yoshida H, Yilmaz CE, Granger DN. Role of tumor necrosis factor-α in the extraintestinal thrombosis associated with colonic inflammation. Inflamm Bowel Dis. 2011;17:2217–23.
29. deFonseka AM, Tuskey A, Conaway MR, et al. Antitumor necrosis factor-α therapy is associated with reduced risk of thromboembolic events in hospitalized patients with inflammatory bowel disease. J Clin Gastroenterol. 2016;50:578–83.
30. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut. 2011;60:937–43.
31. Hsieh CY, Su CC, Shao SC, et al. Taiwan's National health insurance research database: past and future. Clin Epidemiol. 2019;11:349–58.

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