

Incidence and Risk Factor Analysis of Thromboembolic Events in East Asian Patients With Inflammatory Bowel Disease, a Multinational Collaborative Study

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Background: Inflammatory bowel disease (IBD) increases the risk of venous thromboembolism (VTE) events. However, the incidence and necessity of prophylaxis for VTE in Asian IBD patients is unknown. We examined the incidence of VTE in East Asian IBD patients and analyze the possible risk factors.

Methods: We conducted a multinational retrospective study of 2562 hospitalized IBD patients from 2010 to 2015. Moreover, a nationwide cohort study from 2001 to 2013 from the Taiwan National Health Insurance Research Database (NHIRD) was conducted to analyze the incidence rate of VTE in IBD and non-IBD patients.

Results: In the hospitalized cohort, 24 IBD patients [17 ulcerative colitis (UC) and 7 Crohn's disease (CD)] received a VTE diagnosis (0.9%). These patients had a higher proportion of extensive UC ($P = 0.04$), penetrating-type CD ($P < 0.01$), and bowel operation history ($P = 0.01$). VTE was associated with low hemoglobin ($P < 0.01$), low platelet ($P < 0.01$), and low albumin ($P < 0.01$) levels. For the nation-wide cohort study, 3178 IBD patients and 31,780 age- and sex-matched non-IBD patients were analyzed. The average incidence rate was 1.15 per 1000 person-years in the IBD cohort and 0.51 in the non-IBD cohort. The relative risk was 2.27 (95% CI, 1.99–2.60).

Conclusions: East Asian IBD patients carry a 2-fold increased risk of VTE than the general population. The incidence of VTE in the East Asian IBD patients is still lower than that in Western countries. Therefore, close monitoring rather than routine prophylaxis of VTE in East Asian IBD patients is recommended.

Key words: inflammatory bowel disease, venous thromboembolism event, risk factor

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by a chronic inflammatory process and an overlap with immunological abnormalities, which underlie an increased risk of

thromboembolic events (TEs). The most common types of venous thromboembolism (VTE) event in IBD patients are deep venous thrombosis (DVT) and pulmonary embolism (PE).¹ VTE is a serious extraintestinal manifestation and is associated with high morbidity and mortality rates.² Therefore, the early diagnosis of new IBD cases and control of inflammatory processes are believed to play crucial roles in reducing the risk of TEs.³

In Western countries, thrombotic complications are common in IBD patients. They are 1.5-fold–4-fold more likely to occur in IBD patients than in people without this condition,^{1,2,4–9} and the relative risk (RR) exceeds 15 during disease flares, with an overall incidence rate of 1%–8%.^{4,10–14} Therefore, prophylactic anticoagulants are recommended in IBD patients who have been hospitalized with IBD flares without active or severe bleeding and for moderate to severe IBD flares in outpatients with a history of VTE provoked by an IBD flare or an unprovoked VTE.³ In Western countries, prophylaxis for VTE during admissions for acute IBD flares is considered an indicator of the quality of care for IBD patients,^{1,3,5} whereas in Asian countries, only ≤24% of clinicians provide adequate prophylaxis for VTEs.¹⁵

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Although the underlying causes for the increased risk of thrombus development remain poorly understood, the following factors may contribute to this phenomenon. IBD is associated with several prothrombotic abnormalities, including initiation of the coagulation system, downregulation of natural anticoagulant mechanisms, impairment of fibrinolysis, increased platelet counts, and reactivity and dysfunction of the endothelium.³ Several acquired factors, such as inflammatory activity, hospitalization, surgery, pregnancy, disease phenotype (eg, fistulizing disease, colonic involvement, and extensive involvement), and drug therapy (mainly steroids) are also responsible for the increased risk of VTEs in IBD.^{3,10} All the aforementioned findings have been observed in Western populations, but data for Asian populations are lacking.

The prevention of thromboembolism is mainly aimed at minimizing the acquired/reversible risk factors (eg, inflammation, immobility, hospitalization, steroid therapy, central intravenous catheters, smoking, oral contraceptives, and deficiency of B vitamins and folate).¹⁶ Standardized guidelines for the prophylaxis of thromboembolism in Western IBD were well established, whereas Asian IBD patients appeared not routinely to be prophylactic.¹⁵ The guidelines for Asian IBD patients are urgently needed and should be applied in clinical practice to avoid preventable morbidity and mortality.⁴ Because venous thromboembolism is relatively uncommon in the Asian population compared to that in whites^{17–20} and the exact incidence of VTEs in Asian IBD patients is not clear and no known risk factors for VTEs have been explored in Asian populations, the necessity of and techniques for prevention remain unknown. Therefore, we explored the incidence and risk factors of VTE in East Asian IBD patients in a multinational setting.

MATERIALS AND METHODS

Comparison of IBD Patients with and without VTE

A retrospective analysis was conducted at Tokyo Medical and Dental University (TMDU; Japan), Asan Medical Center (AMC; South Korea), and National Taiwan University Hospital (NTUH; Taiwan). This study was approved by the institutional review boards of the 3 medical centers. We analyzed the incidence of and risk factors for IBD in inpatients through chart reviews of records from 2010 to 2015. Only TE that had been diagnosed through imaging procedures were considered. The imaging procedures included ultrasound, angiography, computed tomography, and lung scan. The patients were included once they were diagnosed with VTE between January 2010 and December 2015. Patients who developed VTEs before the IBD diagnosis and those with cancer were excluded. The data of confounders, including age, sex, smoking, extraintestinal involvement (eg, of the eye, joints, or skin; ankylosing spondylitis; and primary sclerosing cholangitis), comorbidities (eg, hypertension, diabetes mellitus, hyperlipidemia, and atrial

fibrillation), disease activity determined using the Truelove and Witts severity index for ulcerative colitis (UC), extent of disease determined using the Montreal classification, Vienna classification of Crohn's disease (CD; location: L1, terminal ileum; L2, colon; L3, ileocolon; and L4, upper gastrointestinal tract; behavior: B1, nonstricturing nonpenetrating; B2, stricturing; and B3, penetrating), IBD medications (ie, corticosteroids, mesalamine, immunomodulators, and biologics), and laboratory data [including white blood cell and platelet counts and hemoglobin, albumin, and C-reactive protein (CRP) levels] were analyzed. To identify the possible risk factors for VTE, we compared the index patients with control groups of non-VTE IBD patients matched by age (at admission) and sex at a ratio of 1:4.

Comparison of IBD Patients with the General Population

A nationwide cohort study of data from the Taiwan National Health Insurance Research Database (NHIRD) was conducted for the period of January 1, 2001, to December 31, 2013. The NHIRD is maintained and made accessible for scientific research by the National Health Research Institutes, Taiwan. The National Health Insurance program covers nearly 99% of the entire population of Taiwan (approximately 23 million persons). We used International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM) codes for the detection of UC (ICD-9-CM code 556.9), CD (ICD-9-CM code 555.9), PE (ICD-9-CM code 415.1), and DVT (ICD-9-CM code 453). We also used the Registry for Catastrophic Illness Patient Database (RCIPD), a subset of the NHIRD, as another filter to confirm the accuracy of the IBD diagnosis. Only patients who received a catastrophic illness certificate were registered in this system. Comprehensive medical information, including the data of sex, age, disease diagnosis, history of surgery, and medication usage, was retrieved from the NHIRD. To maintain patient privacy, the original identification numbers are removed from the NHIRD data before release.

Statistical Analysis

Results are expressed as the median and range. Chi-square and Fisher exact tests were used to compare categorical variables among IBD patients with VTE. Wilcoxon rank sum test, Student *t* test, and ANOVA were used for continuous variables. The incidence rate is presented per 1000 person-years. Poisson regression was used to calculate the relative risk (RR) and 95% confidence intervals (CIs) from the NHIRD data. These analyses were performed using SAS (SAS, Cary, NC, USA). A *P* value of < 0.05 was considered significant.

Ethical Considerations

This study was approved by the institutional review boards of the Tokyo Medical and Dental University (TMDU;

Japan), Asan Medical Center (AMC; South Korea), and National Taiwan University Hospital (NTUH; Taiwan).

RESULTS

Demographic Characteristics of the Patients

The data from 2010 to 2015 for 2562 hospitalized IBD patients from the 3 medical centers were reviewed. The number of hospitalized IBD patients at TMDU was 408 (n = 245 for UC and n = 163 for CD), at AMU was 1789 (n = 592 for UC and n = 1197 for CD), and at NTUH was 365 (n = 178 for UC and n = 187 for CD). The IBD patients in this cohort were mostly in young age (1–95, mean: 32.6). Women accounted for a minority in this multicenter study (M:F = 1624:938). The incidence proportion of VTE was 1.01% (18/1789), 0.74% (3/408), and 0.82% (3/365) at AMC, TMDU, and NTUH, respectively. In subsequent analyses, all the data were pooled (Table 1).

Among these patients, 1547 were diagnosed with CD and 1015 with UC. Overall, 24 patients (0.94%; n = 17 for UC and n = 7 for CD) with VTE were identified. The median age of these patients at VTE diagnosis was 45.4 years (range: 17 years–81 years). The median age at IBD diagnosis was 36.5 years (range: 16.5 years–76 years). The median time interval from the diagnosis of IBD to the first VTE diagnosis was 5.5 years (range: 1 month to 30 years).

A total of 938 patients were women (36.6%). Women were predominant in the VTE group (54.2%), but this finding was not statistically significant ($P = 0.07$). In the UC group, patients with VTE were older than those without VTE ($P = 0.01$; Supplementary Table 1).

The clinical characteristics and outcomes for the 24 studied patients are listed in Table 2. In this cohort, 15 patients (62.5%) were diagnosed with PE and 18 (75%) with DVT. Thirteen patients (54%) received systemic corticosteroids for VTEs. Only 1 patient did not receive anticoagulation treatment because of an absence of symptoms and an incidental diagnosis performed through computed tomography. Three patients expired, and 1 of them died because of refractory retroperitoneal abscess-related sepsis. Three patients (3/24, 12.5%) had recurrent VTE after treatment.

Risk Factors Associated with VTE

For each VTE patient, controls were randomly selected from the hospitalized IBD populations and matched by age (at admission) and sex at a ratio of 1:4. The estimated total number of person-years of follow-up in this study was 33,339. As the VTE event was 24, the overall incidence of VTE in the 3 centers was 0.72 per 1000 person-years. Further stratified analysis indicated that the incidence of VTE was 0.69 per 1000 person-years in the UC group and 0.79 per 1000 person-years in the CD group. Compared with non-VTE IBD patients, those with VTE were associated with a higher proportion of bowel operation history (12/24 vs 22/95, $P = 0.01$), extensive UC (12/16 vs 34/68, $P = 0.04$), and penetrating-type CD (B3; 7/7 vs 9/28, $P < 0.01$). The underlying comorbidities or extraintestinal manifestations of patients with VTE did not differ significantly from those of patients without VTE (Table 3). VTE was also associated with low hemoglobin ($P < 0.01$), low platelet ($P < 0.01$), low albumin ($P < 0.01$), and high CRP levels ($P < 0.01$; Table 3).

Multivariate analysis revealed that the bowel operation history, low platelet, and low albumin were independent predictors of VTE (Table 4). Due to the small case number, UC location or CD behavior were not further analyzed in the multivariate analysis.

Detection of VTE in the NHIRD

A total of 3178 patients who received a diagnosis of IBD from 2001 to 2013 were screened and registered as having a catastrophic illness in the NHIRD; 686 (21.6%) patients were diagnosed with CD and 2492 (78.4%) with UC. Overall, 62.8% of the patients were men, and only 21 patients (0.66%) had ever received a VTE diagnosis. The 3178 patients with IBD were age- and sex-matched with 31780 non-IBD patients. The incidence rates were 1.15 and 0.51 per 1000 person-years in the IBD and non-IBD cohorts, respectively. The RR was 2.27 (95% CI, 1.99–2.60). The IBD patients were twice as likely to develop DVT (RR, 2.24; 95% CI, 1.95–2.25) and PTE (RR, 2.32; 95% CI, 2.03–2.65) than were the non-IBD patients. Women in the IBD cohort were at a higher risk of VTE than were the men. The risk of VTE increased with age in both the IBD and non-IBD groups (Table 5).

TABLE 1: Baseline Characteristics of IBD Patients from 3 Medical Centers

	AMC	TMDU	NTUH	Overall
Number	1789	408	365	2562
Age at admission	25 (6–78)	37 (1–95)	40.5 (1–94)	32.6 (1–95)
VTE	18 (1.01%)	3 (0.74%)	3 (0.82%)	24 (0.94%)
Gender (Woman)	626 (35%)	165 (40.4%)	147 (40.3%)	938 (36.6%)

IBD, inflammatory bowel disease; AMC, Asan Medical Center; TMDU, Tokyo Medical and Dental University; NTUH, National Taiwan University Hospital; VTE, venous thromboembolism.

TABLE 2: Clinical Features of IBD Patients With VTE

	VTE type	Age of VTE	Symptoms	IBD Medication	Treatment	Outcome	Recurrence
1	PTE + DVT	75	Lt. leg swelling	Mesalazine	Heparin + Coumadin	survive	yes
2	DVT	65	Lt. leg swelling	Sulfasalazine	rivaroxaban	survive	no
3	PTE + DVT	42	Lt. leg swelling	Steroid	Heparin + Coumadin	survive	no
4	PTE + DVT	57	No	Mesalazine +steroid	IVC filter + Heparin + Coumadin + rivaroxaban	survive	no
5	DVT	42	Rt. leg swelling	Sulfasalazine	Heparin + Coumadin	survive	yes
6	PTE + DVT	43	Rt. leg pain	Azathioprine+ steroid	IVC filter + Heparin + Coumadin	survive	no
7	PTE	26	No	Mesalazine +steroid	No	survive	no
8	PTE	41	No	Balsalazide	Heparin + Coumadin	survive	no
9	PTE + DVT	68	Leg swelling, dyspnea	Azathioprine+biologics	Heparin + rivaroxaban	survive	no
10	DVT	60	Hematochezia	No	Heparin + Coumadin	survive	no
11	PTE + DVT	37	Abdominal pain	Mesalazine +steroid	IVC filter+ Heparin + Coumadin	survive	no
12	PTE	34	Dyspnea	No	Heparin	survive	no
13	PTE	35	Dyspnea	Mesalazine +steroid	IVC filter + Heparin + Coumadin	survive	no
14	PTE + DVT	81	Fever	Mesalazine + steroid + azathioprine +biologics	Heparin	Expired	no
15	DVT	41	Leg swelling	Steroid	Heparin + Coumadin	survive	no
16	PTE	24	Dyspnea	Steroid	Heparin + Coumadin	survive	no
17	DVT	23	Abdominal pain	Azathioprine+ steroid	Balloon/ stent + Heparin + Coumadin	survive	no
	VTE type	Age of VTE	Symptoms	IBD medication	Treatment	Outcome	Recurrence
18	PTE	67	Hematochezia	Mesalazine + steroid	Heparin	Expired	no
19	DVT	52	Rt. arm swelling	Mesalazine	IVC filter+ Heparin	survive	No
20	DVT	50	Rt. arm swelling	Mesalazine	IVC filter+ Heparin + Coumadin	survive	No
21	DVT	67	Both legs swelling	Mesalazine + steroid	IVC filter+ Heparin + Coumadin	Expired	No
22	PTE+DVT	48	Leg swelling	Adalimumab	IVC filter+ Heparin + Coumadin	survive	yes
23	PTE + DVT	17	Dyspnea	Mesalazine	Heparin + Coumadin	survive	no
24	DVT	51	Leg swelling	Mesalazine + steroid	Heparin + Coumadin	survive	no

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; VTE, venous thromboembolism

Seven patients were diagnosed with VTE in the CD cohort and 96 patients in the non-IBD cohort. The incidence rate was 2.07 per 1000 person-years in the CD cohort and 0.51 in the non-IBD cohort. A comparison of the CD and non-IBD groups revealed a RR of 4.53 (95% CI, 3.67–5.58) for VTE. The CD patients exhibited an approximately 5-fold increased risk of DVT (RR, 5.04; 95% CI, 4.10–6.19) and nearly twice the risk of PTE (RR, 1.95; 95% CI, 1.44–2.64) than did the non-IBD patients (Table 6).

Fourteen patients were diagnosed with VTE in the UC cohort. The incidence rate was 0.94 per 1000 person-years. The

RR was 1.82 (95% CI, 1.56–2.60). A subanalysis revealed that the RRs for DVT (1.68; 95% CI, 1.42–1.98) and PTE (2.40; 95% CI, 2.08–2.76) were both higher in the UC cohort than in the non-IBD cohort (Table 6).

DISCUSSION

To the best of our knowledge, this is the first multinational study to examine the incidence and risk factors of VTE in Asian IBD patients. Our results demonstrate that, compared with the risk in Western countries, the VTE risk is lower in general East Asian populations and hospitalized IBD patients,

TABLE 3: Baseline Clinical and Laboratory Variables in Patients with and without VTE

Variables, No. (%)	VTE(+) (n = 24)	VTE(-) (n = 96)	-value _a
IBD type			
CD	7 (29.2)	28 (29.2)	
UC	17 (70.8)	68 (70.8)	
Smoking			
Nonsmoker	14 (58.3)	69 (71.9)	0.20
Ever-smoker	10 (41.7)	27 (28.1)	
Extra-GI			
Eye	0 (0.0)	1 (1.2)	1.00
Joint	2 (8.3)	9 (10.3)	1.00
Skin	1 (4.2)	3 (3.5)	1.00
AS	0 (0.0)	0 (0.0)	NA
PSC	1 (4.2)	0 (0.0)	0.22
Comorbidity			
Atrial fibrillation	0 (0.0)	1 (1.4)	1.00
Hypertension	2 (8.3)	13 (18.3)	0.34
Diabetes	2 (8.3)	4 (5.6)	0.64
Hyperlipidemia	0 (0.0)	1 (1.4)	1.00
Bowel operation			
	12 (50.0)	22 (23.2)	0.01
Laboratory data			
	n = 24	n = 94 _b	Pvalue _c
Hemoglobin (g/dL)	9.83 ± 1.92	11.95 ± 2.28	<0.01
White blood cell (k/μL)	8.44 ± 4.12	7.15 ± 3.64	0.28
Platelet (K/μL)	246 ± 92	335 ± 165	<0.01
Albumin (g/dL)	2.5 ± 0.93	3.4 ± 0.97	<0.01
C-reactive protein (mg/dL)	4.91 ± 6.19	2.13 ± 3.85	<0.01
Variables, No. (%)	VTE(+) (n = 24)	VTE(-) (n = 96)	Pvalue _a
UC Severity (n = 17)			
Mild	5 (29.4)	31 (54.4)	0.19
Moderate	9 (52.9)	19 (33.3)	
Severe	3 (17.7)	7 (12.3)	
UC location			
E1	0 (0.0)	19 (27.9)	0.04
E2	4 (25.0)	15 (22.1)	
E3	12 (75.0)	34 (50.0)	
CD location (n = 7)			
L1	0 (0.0)	8 (29.6)	0.13
L2	0 (0.0)	4 (14.8)	
L3	7 (100.0)	15 (55.6)	
L4	4 (66.7)	9 (37.5)	
CD Behavior			
B1	0 (0.0)	11 (39.3)	0.07
B2	0 (0.0)	7 (25.0)	0.30
B3	7 (100.0)	9 (32.1)	<0.01

GI, gastrointestinal; AS, ankylosing spondylitis; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; VTE, venous thromboembolism; UC, ulcerative colitis; CD, Crohn's disease

_a Fisher's exact test.

_b Laboratory data of 2 non-VTE patients were missing.

_c Through the Wilcoxon 2-sample test

TABLE 4: Univariate and Multivariate Analysis of Risk Factors of VTE in Multicenter IBD Patients

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
IBD Type CD vs UC	1.00 (0.37, 2.68)	1.00		
Smoking	1.83 (0.72, 4.61)	0.20		
Extra-GI	1.25 (0.36, 4.3)	0.72		
Comorbidity	0.35 (0.07, 1.66)	0.19		
Bowel operation	3.32 (1.31, 8.42)	0.01	2.12 (0.66, 6.89)	<0.01
Hemoglobin (g/dL)	0.63 (0.50, 0.81)	<0.01	0.57 (0.41, 0.78)	0.21
White blood cell (k/ μ L)	1.06 (0.95, 1.19)	0.28		
Platelet (K/ μ L)	0.99 (0.99, 1)	<0.01	0.99 (0.99, 1)	<0.01
Albumin (g/dL)	0.44 (0.27, 0.70)	<0.01	0.64 (0.37, 1.11)	<0.01
C-reactive protein (mg/dL)	1.12 (1.02, 1.22)	<0.01	1.04 (0.91, 1.18)	0.11

VTE, venous thromboembolism; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; GI, gastrointestinal.

The multivariate analysis only included the variables which *P* value < 0.05 in univariate analysis.

although we did observe a 2-fold increase in VTE risk in IBD patients compared with the general population.

In the general population, the incidence of VTE is 1.03–1.49 per 1000 person-years among Europeans in North America and Europe and 0.21–0.29 per 1000 person-years in Asian populations.^{17, 21, 22} The crude incidence of symptomatic VTE in the general population in Taiwan is 0.17 per 1000 person-years.²³ Two meta-analyses revealed that IBD patients exhibit a 2.20- to 2.85-fold higher risk of VTE than do non-IBD populations.^{5, 24} In the present study, the assessment of data from the NHIRD indicated that the incidence rate of VTE is 0.51 per 1000 person-years in the general population and 1.15 per 1000 person-years in IBD patients. Compared with the non-IBD patients, IBD patients are at an approximately 2-fold increased risk of VTE.

Regarding IBD patients, necropsy studies have shown that the incidence of VTE in Western countries varies between 1% and 8%, reaching up to 39%.^{4, 12} In the United Kingdom, the overall incidence of VTE is 2.6 per 1000 person-years and 25.2 per 1000 person-years during hospitalization periods.¹⁴ In our international multicenter hospitalized IBD cohort, the overall incidence was 0.72 per 1000 person-years. Because the incidence of VTE—both in the general population and IBD patients—is lower among Asian populations than among Western populations, the absolute number of VTE events in IBD patients would be low, which is compatible with our current practice that no prophylaxis for VTE might be reasonable. However, we still recommend close monitoring of the symptoms in hospitalized IBD patients because there is still an increased risk of VTE in these patients.

Both the entire IBD population (from the Taiwan NHIRD) and hospitalized cohort (multicenter cohorts) exhibited a higher incidence of VTE in the CD group than

in the UC group. The Swiss IBD Cohort Study reported that the VTE prevalence was 3.4% (45/1324) in CD patients and 4.7% (45/960) in UC patients,²⁵ whereas other studies have reported similar risks of VTE between UC and CD patients.^{11, 24}

We determined that among IBD patients, women are at an increased risk of VTE. In the Mediterranean region, women and older individuals are predominant among patients with VTE.²⁶ Several studies also have demonstrated a higher incidence of VTE among women of childbearing age, whereas the overall incidence of VTE does not differ consistently between women and men.^{27, 28} The role of sex in VTE remains uncertain. However, the use of hormone replacement therapy and oral contraceptives (OC), and pregnancy all increase the risk of VTE among women. The odds ratio was 5-fold to 6-fold for pregnancy²⁹ and 3-fold to 6-fold for patient who received OC in epidemiological study.³⁰ As there was no patient pregnant nor one who used OC or hormone replacement therapy in our index cases, we didn't further explore the impact of hormone therapy on VTE.

Smoking is a major risk factor for acute coronary thrombosis, but its role in VT is still controversial. Smoking was shown to be a risk factor for DVT in Chinese neurosurgical patients³¹ but not an independent risk factor in orthopedic trauma surgery patients.³² Our results reveal that smoking is unassociated with VTE in East Asian IBD patients.

We found that the disease extent correlated with the VTE risk in UC and disease behavior in CD. Solem et al revealed that 76% of UC patients who experience VTE have pancolonic disease.³³ Alatri also reported that pancolitis is significantly associated with VTE in UC patients.³⁴ In our study, 70.6% of the UC patients with VTE had pancolitis, and all the CD patients with VTE had ileocolon involvement. Active fistulizing disease was

TABLE 5: Incidence and Crude RR of VTE, DVT, and PTE Stratified by Sex and Age in the IBD and Non-IBD Cohorts

	IBD (N = 3178)			n	Non-IBD (N = 31780)		RR _a (95% CI)
	N	Follow-up person-year	Rate, per 1000 person-year		Follow-up person-year	Rate, per 1000 person-year	
VTE	21	18269.2	1.15	96	187327.4	0.51	2.27 (1.99–2.60)
By gender							
Male	10	11347.3	0.88	58	116036.2	0.50	1.76 (1.46–2.11)
Female	11	6778.5	1.62	38	70031.4	0.54	3.11 (2.55–3.80)
By age, year							
= <39	5	8480.1	0.59	12	83354.2	0.14	4.26 (3.58–5.06)
40–59	10	7172.0	1.39	29	74614.7	0.39	3.64 (3.01–4.39)
> = 60	6	2617.2	2.29	55	29358.6	1.87	1.15 (0.78–1.70)
DVT	16	18278.0	0.88	74	187370.0	0.39	2.24 (1.95–2.57)
By gender							
Male	7	11348.9	0.62	45	116062.0	0.39	1.59 (1.31–1.93)
Female	9	6785.6	1.33	29	70048.1	0.41	3.29 (2.68–4.03)
By age, year							
= <39	4	8481.2	0.47	8	83362.8	0.10	5.11 (4.31–6.06)
40–59	6	7179.6	0.84	20	74641.5	0.27	3.13 (2.54–3.84)
> = 60	6	2617.2	2.29	46	29365.7	1.57	1.38 (0.95–2.00)
		IBD (N = 3178)			Non-IBD (N = 31780)		RR * (95% CI)
	N	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
PTE	7	18341.1	0.38	31	187489.7	0.17	2.32 (2.03–2.65)
By gender							
Male	4	11371.7	0.35	18	116148.8	0.15	2.26 (1.90–2.68)
Female	3	6825.9	0.44	13	70081.1	0.19	2.43 (1.97–3.00)
By age, year							
= <39			0.24	6	83382.4	0.07	3.38 (2.80–4.08)
40–59			0.55	10	74675.8	0.13	4.18 (3.50–5.00)
> = 60			0.38	15	29431.5	0.51	0.68 (0.42–1.12)

^aThrough Poisson regression.

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; VTE, venous thromboembolization; RR, relative risk

a risk factor for VTE in CD patients.³⁵ We also observed that penetrating-type CD is highly associated with VTE.

In addition to the disease extent and behavior, we observed that low hemoglobin, low platelet, low albumin, and high CRP levels are risk factors for VTE in East Asian IBD patients. These parameters, which may represent disease severity, are associated with VT.

In this study, 54% of patients received corticosteroids for VTE. This type of medication can induce hypercoagulability by increasing the levels of plasminogen activator inhibitor and coagulation factors FVII, VIII, and XI³⁶ and by inhibiting prostacyclin syntheses.³⁷ Compared with biologic agents, corticosteroids are associated with a 5-fold increased risk of VTE.³⁸ Patients who receive steroids should be monitored for thrombotic complications. In our study, 50% of the patients with VTE

had a surgical history. Merrill et al also reported that surgery is an independent risk factor for TE in patients with IBD.³⁹ In a study by Bollen, 40% of patients with VTE underwent surgery within 6 months before the event.⁴⁰

A total of 24 VTE events were identified in this study, and the mortality rate was 12.5%. Mortality rates in the range of 8%–22% have been reported among IBD patients after an episode of VTE.^{33,41} Because our sample contained too few mortality cases, we could not analyze the mortality-associated risk factors.

This study had some limitations. First, the patients were retrospectively identified from 3 centers. Second, age is a main risk of VTE^{19,42} and the mean age of our inpatient cohort was young that might contribute to lower incidence of VTE. Third, we only included imaging-proven VTE that might have led to underdiagnosis. Fourth, the follow-up duration in the centers was

TABLE 6: Incidence and Crude RR of VTE, DVT, and PTE Stratified by Sex and Age in the CD/ UC and Non-IBD Cohorts

		CD (N = 686)		Non-IBD (N = 31780)		RR _a (95% CI)	
	n	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
VTE	7	3375.5	2.07	96	187327.4	0.51	4.53 (3.67–5.58)
By gender							
Male	4	2355.9	1.70	58	116036.2	0.50	3.67 (2.79–4.81)
Female	3	999.7	3.00	38	70031.4	0.54	6.95 (4.99–9.68)
By age, year							
= <39			0.94	12	83354.2	0.14	7.02 (5.58–8.83)
40–59			3.17	29	74614.7	0.39	10.96 (8.21–14.64)
> = 60			6.45	55	29358.6	1.87	4.04 (2.10–7.77)
DVT	6	3375.6	1.78	74	187370.0	0.39	5.04 (4.10–6.19)
By gender							
Male			1.70	45	116062.0	0.39	4.73 (3.68–6.08)
Female			2.00	29	70048.1	0.41	6.09 (4.23–8.76)
By age, year							
= <39			0.94	8	83362.8	0.10	10.53 (8.57–12.94)
40–59			2.11	20	74641.5	0.27	10.62 (7.78–14.48)
> = 60			6.45	46	29365.7	1.57	4.83 (2.61–8.93)
		CD (N = 686)			Non-IBD (N = 31780)		RR * (95% CI)
	n	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
PTE			0.29	31	187489.7	0.17	1.95 (1.44–2.64)
By gender							
Male			0.00	18	116148.8	0.15	
Female			1.00	13	70081.1	0.19	6.79 (4.88–9.45)
By age, year							
= <39			0.00	6	83382.4	0.07	
40–59			1.05	10	74675.8	0.13	10.63 (7.99–14.13)
> = 60			0.00	15	29431.5	0.51	
		UC (N = 2492)			Non-IBD (N = 31780)		RR * (95% CI)
	N	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
VTE	14	14893.7	0.94	96	187327.4	0.51	1.82 (1.56–2.60)
By gender							
Male	6	8991.4	0.67	58	116036.2	0.50	1.31 (1.04–1.64)
Female	8	5778.8	1.38	38	70031.4	0.54	2.58 (2.07–3.22)
By age, year							
= <39	3	6360.5	0.47	12	83354.2	0.14	3.37 (2.75–4.13)
40–59	7	6226.0	1.12	29	74614.7	0.39	2.83 (2.29–3.49)
> = 60	4	2307.2	1.73	55	29358.6	1.87	0.85 (0.53–1.35)
DVT	10	14902.3	0.67	74	187370.0	0.39	1.68 (1.42–1.98)
By gender							
Male	3	8993.0	0.33	45	116062.0	0.39	0.84 (0.64–1.11)
Female	7	5785.8	1.21	29	70048.1	0.41	2.91 (2.33–3.62)
By age, year							
= <39			0.31	8	83362.8	0.10	3.37 (2.74–4.15)
40–59			0.64	20	74641.5	0.27	2.31 (1.83–2.92)
> = 60			1.73	46	29365.7	1.57	1.02 (0.65–1.58)

Continued

TABLE 6: Continued

	CD (N = 686)			Non-IBD (N = 31780)			RR _a (95% CI)
	n	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
		UC (N = 2492)			Non-IBD (N = 31780)		RR* (95% CI)
	N	Follow-up person-year	Rate, per 1000 person-year	n	Follow-up person-year	Rate, per 1000 person-year	
PTE	6	14947.3	0.40	31	187489.7	0.17	2.40 (2.08–2.76)
By gender							
Male			0.44	18	116148.8	0.15	2.81 (2.36–3.35)
Female			0.34	13	70081.1	0.19	1.84 (1.44–2.35)
By age, year							
= <39			0.31	6	83382.4	0.07	4.50 (3.73–5.45)
40–59			0.48	10	74675.8	0.13	3.48 (2.86–4.22)
> = 60			0.43	15	29431.5	0.51	0.75 (0.46–1.24)

^a Through Poisson regression.

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; VTE, venous thromboembolization; UC, ulcerative colitis; RR, relative risk.

defined as the period from IBD diagnosis to VTE onset; hence, it represents the overall VTE incidence in IBD patients but not the VTE incidence during hospitalized periods. Fifth, the NHIRD does not contain information regarding the patient lifestyle, IBD activities and involved location, or laboratory data. Nonetheless, the detailed information on the clinical features of IBD in the multicenter cohort diminished this limitation and contributed toward a better risk assessment for VTE in IBD.

CONCLUSIONS

In conclusion, via a multinational collaborative study, we firstly demonstrated the incidence of VTE is lower among East Asian populations than among Western countries, both in the general population and IBD patients. Furthermore, we confirm that bowel operation history, extensive UC, and penetrating-type CD are risk factors for thrombosis. According to our results, close monitoring and paying attention to those with risk factors of VTE, rather than routine prophylaxis of VTE, is recommended when taking care of the East Asian IBD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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