ORIGINAL ARTICLE

Incidence and risk factors for venous thrombosis among patients with inflammatory bowel disease in China: a multicenter retrospective study

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Background/Aims: Risk of venous thrombosis is increased in patients with inflammatory bowel disease (IBD); data on Asian IBD patients is limited and status quo of thrombosis screening and prophylaxis are unknown. Therefore, we aimed to investigate the incidence, screening, prophylaxis, and risk factors for venous thrombosis among Asian IBD patients. **Methods:** Medical files of patients with Crohn's disease (CD) and ulcerative colitis (UC) from 17 hospitals across China between 2011 and 2016 were reviewed for venous thrombosis, use of screening and prophylaxis. A case-control study was performed among hospitalized patients with venous thrombosis and their age-, sex-matched IBD controls hospitalized around the same period; disease characteristics and known provoking factors of venous thrombosis were recorded. Risk factors were analyzed in both univariate and logistic regression analyses. **Results:** A total of 8,459 IBD patients were followed for 12,373 person-year. Forty-six patients (0.54%) had venous thrombosis, yielding an incidence of 37.18 per 10,000 person-year. Incidence increased with age, especially among CD. Less than 20% of patients received screening tests and 35 patients (0.41%) received prophylaxis. Severe disease flare was an independent risk factor for venous thrombosis (odds ratio [95% confidence interval]: CD, 9.342 [1.813–48.137]; UC, 5.198 [1.268–21.305]); past use of steroids and extensive involvement were 2 additional risk factors in CD and UC, respectively. **Conclusions:** Incidence of venous thrombosis in China was 37.18 per 10,000 person-year (0.54%). Use of screening and prophylaxis were rare. Severe disease flare was an independent risk factor for thrombosis among hospitalized patients. (**Intest Res 2021;19:313-322**)

Key Words: Inflammatory bowel disease; Venous thrombosis; Pulmonary embolism

INTRODUCTION

Inflammatory bowel disease (IBD) is a risk factor for venous thrombosis, including deep venous thrombosis of lower extremities (DVT), pulmonary embolism (PE), and thrombosis

of other veins such as intra-abdominal venous thrombosis. Patients with IBD, including Crohn's disease (CD) and ulcerative colitis (UC), have an average of 2- to 4-fold risk for venous thrombosis compared to the healthy population.[1-4] Venous thrombosis results in an increased mortality rate, especially in patients who developed PE.[5,6] The development of venous thrombosis among IBD patients is a multifactorial process that follow the triad of Virchow.[7] Active inflammation further increased such risk, and therefore thromboprophylaxis has been recommended for IBD patients with high risk, in-

cluding hospitalized IBD patients during disease flares.[2]

Studies regarding venous thrombosis among IBD patients mainly come from the Western population. Incidence of venous thrombosis varied across different regions, and for Asian population, it was reported to be lower compared to the West.[8] Though the incidence of IBD in the Asian-Pacific region kept rising over the last decade,[9] venous thrombosis still remains under-recognized in clinical practice in Asia.[10] In recent years, 2 population-based studies investigated venous thrombosis among Asian IBD patients and discovered a relatively lower incidence compared to the Western IBD population.[11,12] Similar epidemiology studies involving large populations are still scarce, and status quo of venous thrombosis screening and prophylaxis among Asian IBD patients remains unknown. Therefore, we aimed to investigate the incidence, status quo of screening and prophylaxis for venous thrombosis among Chinese IBD patients, and also to identify risk factors for venous thrombosis.

METHODS

1. Study Population and Variables

We performed a retrospective analysis of all patients with either CD or UC from 17 tertiary referral hospitals in China between January 2011 and June 2016. Both regular follow-up patients diagnosed with IBD prior to the starting date of the current study and newly-diagnosed patients during the study timeframe were included. Data were obtained by manual reviews of medical documents from each participating hospital. Standardized questionnaires were used for data collection. All questionnaires were completed by designated researchers from the participating hospitals, and then collected by one principal researcher responsible for data curation and subsequent analysis. Demographic features including age and sex, type of IBD, both disease and symptom duration of IBD were recorded. Thrombosis screening, use of prophylaxis, diagnosis and outcomes of venous thrombosis events were also recorded.

A case-control analysis was performed to investigate risk factors for venous thrombosis among hospitalized patients. Hospitalized IBD patients with venous thrombosis were 1:3 matched by sex and age (±3 years) to IBD patients without venous thrombosis who were hospitalized around similar period. Time-dependent information was collected using the index time as reference. The index time referred to the time around venous thrombosis diagnosis for patients with venous thrombosis, or the time at inclusion for control group. Detailed disease history around the index time were reviewed, including body mass index, smoking status, central catheter insertion, history of IBD-related bowel resection, history of cancer, history of venous thrombosis prior to IBD diagnosis, comorbidities including history of heart failure, diabetes, myocardial infarction, and stroke. Known provoking events for venous thrombosis including surgery, cancer or pregnancy within 3 months of index time were also noted.[4] IBD disease behaviors were defined according to the Montreal classification.[13] IBD disease activity was assessed using Mayo score for UC and Crohn's Disease Activity Index (CDAI) score for CD.[14,15] Mayo score of less than 2, or CDAI score of less than 150 were considered disease remission, Mayo score between 3 and 5, or CDAI score between 150 and 220 were considered mildly-active disease, Mayo score between 6 and 10, or CDAI score between 221 and 450 were considered moderately-active disease, Mayo score of more than 11, or CDAI score of more than 450 were considered severely-active disease. IBD-related medication was also noted; past medication referred to treatment received beyond 1 month before the index time, and only medication used for longer than 3 months were included; current medication referred to treatment used within 1 month around index time. Exclusion criteria: (1) incomplete demographic information; (2) unconfirmed diagnosis of IBD according to current guideline; or (3) unknown time for follow-up or patients with only one clinic visit.

2. Definition of Venous Thrombosis

Venous thrombosis refers to thrombosis in the venous system or PE, the former included and not confined to DVT, thrombosis of upper extremities, and intra-abdominal venous thrombosis. Diagnosis of venous thrombosis should be made based on direct evidence from ultrasound, computed tomography or pulmonary angiography. Only events of venous thrombosis that occurred during the study timeframe were counted.

3. Statistical Analysis

Kolmogorov-Smirnov test was used to test for normality of data. Continuous variables with normal distribution were presented with mean ± standard deviations; non-normal variables were reported as medium with interquartile ranges (IQRs). Mean of 2 continuous normally distributed variables were compared using independent t-test; non-normally distributed continuous variables were compared using Mann-Whitney U test. Categorical variables were presented as percentages and compared using chi-square analysis. Hazard ratio was calcu-

lated using Cox-proportional regression analysis. Fisher exact test was used when sample size was under 5. All variables with $P<0.1$ in the univariate analysis were entered in a stepwise manner into the logistic regression. A P-value of <0.05 was considered statistically significant. All analysis was conducted using SPSS software version 22 (IBM Corp., Armonk, NY, USA).

4. Ethical Statement

This study was approved by Institutional Review Board of the Sir Run Run Shaw Hospital (IRB No. 20200721-33). The informed consent was waived.

RESULTS

1. Baseline Characteristics and Incidence of Venous Thrombosis

A total of 8,459 patients were eventually included, median time of follow-up was 9.6 months (IQR, 1.0–17.8 months). Forty-six patients (0.54%) were identified as having venous thrombosis, yielding an incidence of 37.18 per 10,000 person-year (total follow-up of 12,373 person-year) for venous thrombosis. Demographic characteristics of patients with and without venous thrombosis are shown in Table 1. Patients with venous thrombosis were older compared to control. Sex, type of IBD, disease and symptom duration did not differ between patients with and without venous thrombosis.

Among all types of venous thrombosis, incidence of DVT was highest (0.33%, 22.63 per 10,000 person-year), and PE

Table 1. Baseline Characteristics of All Patients

Variable	With thrombosis (n = 46)	Without thrombosis (n = 8,413)	P-value[a]
Male sex	26 (56.5)	5,282 (62.8)	0.445
Age (yr)	46.3 ± 15.7	39.9 ± 15.0	0.004
< 40	17 (37.0)	4,556 (54.2)	
40–59	18 (39.1)	2,873 (34.1)	
≥ 60	11 (23.9)	984 (11.7)	
Type of IBD (CD)	20 (43.5)	4,102 (48.8)	0.555
Disease duration (mo)	39.1 (5.3–58.5)	21.6 (4.0–51.7)	0.123
Symptom duration (mo)	53.4 (20.5–111.8)	48.7 (22.1–81.2)	0.465

Values are presented as number (%), mean ± standard deviation, or median (interquartile range).
[a]$P<0.05$, compared to patients without venous thrombosis.
IBD, inflammatory bowel disease; CD, Crohn's disease.

was lowest (0.08%, 5.66 per 10,000 person-year). The combined incidence of DVT and PE was 28.29 per 10,000 person-year. Incidence of venous thrombosis increased with age; such trend was most significant for DVT, and for patients with CD in particular. Comparing patients over 60 years old to patients under 40 years old, the hazard ratio for venous thrombosis and DVT were 2.776 and 3.343, respectively, which increased to 3.779 and 4.738 for patients with CD in particular and became insignificant for patients with UC. Risk of thrombosis other than DVT and PE did not differ among different age groups (Table 2).

2. Screening, Prophylaxis, Treatment and Outcome for Venous Thrombosis

A total of 1,633 patients (19.3%) received D-dimer tests, 201 patients (2.38%) received ultrasound screening, and 24 patients (0.28%) received computed tomography scan for screening. Thirty-five patients (0.41%) received prophylaxis including warfarin, heparin or low molecular weight heparin and none of these patients developed venous thrombosis. Among the 46 patients diagnosed with venous thrombosis, 28 patients developed DVT without progression to PE, 7 patients developed PE, and 11 patients had venous thrombosis of other veins (Table 3). Thirty-five patients (76%) reported symptoms in accordance with the affected veins, including swollen of the affected limbs, chest pain, or abdominal pain; 11 patients did not report any symptoms. Six out of 46 patients were diagnosed as outpatients and no details for treatment and outcome were recorded. Among the 40 patients being hospitalized, the median time of hospitalization was 27 days (IQR, 14–28 days). Duration of hospitalization was longer for patients over 60 years compared to patients under 60 years old (23 days [IQR, 12–35] vs. 39 days [IQR, 30–44], $P=0.033$). No differences in hospitalization duration were observed between CD and UC (31 days [IQR, 15–39] vs. 23 days [IQR, 13–38], $P=0.632$), male and female (21 days [IQR, 11–35] vs. 34 days [IQR, 19–39], $P=0.133$), or between DVT and PE (31 days [IQR, 15–39] vs. 34 days [IQR, 9–94], $P=0.971$). Six patients lost follow-up after discharge, 32 patients had complete recovery from venous thrombosis, 1 patient progressed to pulmonary hypertension, and 1 patient with CD died due to PE.

3. Risk Factors Associated with Venous Thrombosis among Hospitalized Patients

Hospitalized patients with venous thrombosis were matched to patients without venous thrombosis (Tables 4, 5). None of

Table 2. Incidence of Venous Thrombosis as Stratified by IBD Diagnosis, Type of Thrombosis and Age Group

Type of thrombosis	IBD			CD			UC		
	No. (%)	Incidence[a]	HR (95% CI)[b]	No. (%)	Incidence[a]	HR (95% CI)[b]	No. (%)	Incidence[a]	HR (95% CI)[b]
All									
All age	46 (0.54)	37.18	-	20 (0.49)	30.75	-	26 (0.60)	44.31	-
<40 yr	17 (0.37)	25.50	1	9 (0.31)	19.97	1	8 (0.49)	37.05	1
40–59 yr	18 (0.62)	43.39	1.658 (0.853–3.222)	7 (0.71)	44.09	1.939 (0.718–5.234)	11 (0.58)	42.96	1.179 (0.474–2.934)
≥60 yr	11 (1.11)	70.62	2.776 (1.294–5.955)[e]	4 (1.97)	97.65	3.779 (1.123–12.715)[d]	7 (0.88)	60.98	1.762 (0.634–4.903)
DVT									
All age	28 (0.33)	22.63	-	13 (0.32)	19.98	-	15 (0.35)	25.56	-
<40 yr	11 (0.24)	16.50	1	6 (0.20)	13.31	1	5 (0.31)	23.16	1
40–59 yr	8 (0.28)	19.29	1.122 (0.451–2.795)	4 (0.41)	25.20	1.660 (0.466–5.908)	4 (0.21)	15.62	0.680 (0.182–2.533)
≥60 yr	9 (0.90)	57.78	3.343 (1.380–8.102)[e]	3 (1.48)	73.24	4.738 (1.173–19.134)[d]	6 (0.76)	52.27	2.292 (0.697–7.540)
PE									
All age	7 (0.08)	5.66	-	4 (0.10)	6.15	-	3 (0.07)	5.11	-
<40 yr	2 (0.04)	3.00	1	1 (0.03)	2.22	1	1 (0.06)	4.63	1
40–59 yr	3 (0.10)	7.23	2.1172 (0.361–13.054)	2 (0.20)	12.60	4.457 (0.394–50.406)	1 (0.05)	3.91	0.793 (0.050–12.715)
≥60 yr	2 (0.20)	12.84	3.978 (0.556–28.481)	1 (0.49)	24.41	5.682 (0.293–110.140)	1 (0.13)	8.71	1.708 (0.106–27.457)
Other[c]									
All age	11 (0.13)	8.89	-	3 (0.07)	4.61	-	8 (0.18)	13.63	-
<40 yr	4 (0.09)	6.00	1	2 (0.07)	4.44	1	2 (0.12)	9.26	1
40–59 yr	7 (0.24)	16.88	2.943 (0.860–10.069)	1 (0.10)	6.30	1.474 (0.133–16.338)	6 (0.31)	23.43	2.636 (0.532–13.064)
≥60 yr	0	0	-	0	0	-	0	0	-

[a]Incidence were displayed in term of 10,000 person-year.
[b]HR used patients under 40 years old as reference group.
[c]Other included intra-abdominal thrombosis, deep venous thrombosis of upper extremities.
[d]P<0.05; [e]P<0.01, compared to the reference group.
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HR, hazard ratio; CI, confidence interval; DVT, deep venous thrombosis of lower extremities; PE, pulmonary embolism.

Table 3. Location of Venous Thrombosis

Type of thrombosis	Location	No. of patients
DVT (n = 28)	Lower limbs	26
	Lower limbs + inferior vena cava/portal vein	2
PE (n = 7)	Pulmonary artery + lower limbs	6
	Pulmonary artery + upper limbs	1
Others (n = 11)	Portal vein	3
	Mesenteric vein	1
	Splenic vein	1
	Inferior vena cava	1
	Portal vein + mesenteric vein	3
	Upper limb + jugular vein	1
	Upper limb + subclavian vein	1

DVT, deep venous thrombosis of lower extremities; PE, pulmonary embolism.

patients reported venous thrombosis prior to the diagnosis of IBD, use of oral contraceptive, or cancer within 3 months of venous thrombosis diagnosis. For CD patients, neither disease location nor disease behavior differed between patients with and without venous thrombosis, whereas for UC patients, those with venous thrombosis were more likely to have pancolitis.

Most of patients had disease flares regardless of venous thrombosis diagnosis (Fig. 1), and the 2 groups did not differ in the proportion of patients in remission. Patients with venous thrombosis were more likely to have severe disease flares, and disease activity scores were generally higher among patients with venous thrombosis compared to control (CDAI score for CD: 325.0 ± 148.1 vs. 203.4 ± 65.8, $P < 0.01$; Mayo score for UC: 11 [9–12] vs. 7 [6–9], $P < 0.01$). In both the univariate and multivariate logistic regression analysis (Table 6), severe disease flare was an independent risk factor for venous thrombosis, regardless of the underlying IBD diagnosis. For CD patients, past use of steroids was an additional independent risk factor for venous thrombosis; the rest variables that were significant in the univariate analysis became insignificant, including history of cancer ($P = 0.999$), comorbidity ($P = 0.999$), past use of steroids ($P = 0.597$), and past use of immunosuppressants ($P = 0.702$). For UC patients, extensive disease involvement was an additional independent risk factors for venous thrombosis; the rest variables that were significant in the univariate analysis became insignificant, including central catheter insertions ($P = 0.285$), history of IBD-related bowel re-

Table 4. Univariate Analysis of Risk Factors for Venous Thrombosis among CD Patients

Variable	Thrombosis (n = 16)	Control (n = 48)	P–value
Age (yr)	41.1 ± 17.5	37.7 ± 12.8	0.419
Male sex	11 (69)	33 (69)	1.000
BMI (kg/m^2)	18.0 ± 3.1	18.8 ± 3.0	0.406
Surgery within 3 months	2 (13)	4 (9)	0.348
Pregnancy within 3 months	0	0	1.000
History of cancer	2 (13)	1 (2)	0.061
Active smoker	1 (6)	7 (15)	0.667
Central catheter insertion	1 (6)	0	0.267
History of IBD-related bowel resection	8 (50)	13 (27)	0.126
Comorbidity	5 (31)	3 (6)	0.019
Disease location			0.257
Terminal ileum	6 (37)	20 (42)	
Colon	0	6 (13)	
Ileocolon	10 (63)	22 (46)	
Upper gastrointestinal tract involvement	1 (6)	6 (13)	0.669
Disease behavior			0.150
Inflammatory	4 (25)	22 (46)	
Stricturing	7 (44)	17 (35)	
Penetrating	5 (31)	6 (13)	
Perianal disease	1 (6)	9 (19)	0.430
Disease remission	3 (19)	21 (44)	0.342
Severe disease flare	7 (44)	4 (8)	0.003
Past IBD medication			
Aminosalicylic acid	9 (56)	27 (56)	1.000
Steroids	11 (69)	18 (38)	0.043
Immunosuppressants	10 (63)	18 (38)	0.092
Biologics	4 (25)	12 (25)	1.000
Current IBD medication			
Aminosalicylic acid	0	6 (13)	0.321
Steroids	4 (27)	4 (8)	0.084
Immunosuppressants	5 (33)	9 (19)	0.274
Biologics	1 (7)	6 (13)	1.000

Values are presented as mean ± standard deviation or number (%). Body mass index (BMI) were missing for 2 Crohn's disease (CD) patients with venous thrombosis; history of surgery within 3 months were missing for 1 CD patients with venous thrombosis and 2 control CD patients; history of cancer were missing for 1 CD patients with venous thrombosis and 1 control CD patients; central catheter insertion were missing for 4 control CD patients; disease behavior were missing for 3 control CD patients; current use of inflammatory bowel disease (IBD) medication were missing for 1 CD patients with venous thrombosis.

section ($P = 0.204$), past use of aminosalicylic acid ($P = 0.405$), and current use of steroids ($P = 0.986$).

Table 5. Univariate Analysis of Risk Factors for Venous Thrombosis among UC Patients

Variable	Thrombosis (n = 24)	Control (n = 72)	P-value
Age (yr)	47.2 ± 14.7	46.0 ± 16.6	0.760
Male sex	12 (50)	36 (50)	1.000
BMI (kg/m^2)	20.9 ± 3.5	21.2 ± 3.3	0.783
Surgery within 3 months	4 (17)	3 (4)	0.167
Pregnancy within 3 months	1 (4)	0	0.253
History of cancer	0	1 (1)	1.000
Active smoker	4 (17)	11 (15)	1.000
Central catheter insertion	3 (13)	0	0.020
History of IBD-related bowel resection	3 (13)	2 (3)	0.098
Comorbidity	4 (17)	11 (15)	1.000
Disease location			0.008
Proctitis	1 (4)	17 (23)	
Left-sided colitis	2 (8)	19 (26)	
Pancolitis	21 (88)	36 (49)	
Disease remission	0	2 (3)	1.000
Severe disease flare	10 (48)	8 (11)	0.001
Past IBD medication			
Aminosalicylic acid	12 (52)	62 (86)	0.001
Steroids	12 (52)	30 (42)	0.471
Immunosuppressants	2 (9)	6 (8)	1.000
Biologics	1 (5)	1 (1)	0.428
Current IBD medication			
Aminosalicylic acid	11 (48)	36 (50)	0.815
Steroids	13 (57)	13 (18)	0.001
Immunosuppressants	2 (9)	4 (6)	0.630
Biologics	0	0	1.000

Values are presented as mean ± standard deviation or number (%). Body mass index (BMI) were missing for 5 ulcerative colitis (UC) patients with venous thrombosis and 9 control UC patients; history of surgery within 3 months were missing for 1 UC patients with venous thrombosis and 1 control UC patients; central catheter insertion were missing for 11 control UC patients; disease severity were not assessed for 3 UC patients with venous thrombosis; past use of inflammatory bowel disease (IBD) medication were missing for 1 UC patients with venous thrombosis; current use of IBD medication were missing for 2 UC patients with venous thrombosis.

DISCUSSION

In this multicenter hospital-based study we reported an incidence of 37.18 per 10,000 person-year (0.54%) for venous thrombosis among Chinese IBD patients. Risk for venous thrombosis was highest among older patients, especially patients with CD. Thrombosis screening was not routinely per-
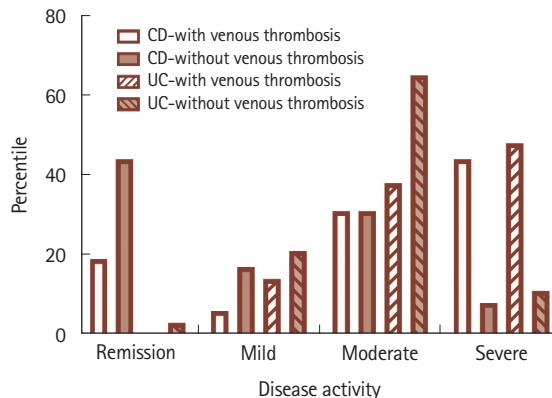

Fig. 1. Disease activity for Crohn's disease (CD), ulcerative colitis (UC) patients with and without venous thrombosis. Disease activity was assessed using Mayo score for UC and Crohn's Disease Activity Index (CDAI) score for CD. Mayo score of ≤ 2, or CDAI score < 150 were considered disease remission, Mayo score between 3 and 5, or CDAI score between 150 and 220 were considered mildly-active disease, Mayo score between 6 and 10, or CDAI score between 221 and 450 were considered moderately-active disease, Mayo score of more than 11, or CDAI score of more than 450 were considered as severe disease activity.

Table 6. Multivariate Logistic Regression of Risk Factor for Venous Thrombosis among IBD Patients

Variable	OR (95% CI)	P-value
CD		
Severe disease flare (yes vs. no)	9.342 (1.813–48.137)	0.008
Past use of steroids (yes vs. no)	5.672 (1.331–24.165)	0.019
UC		
Extensive involvement (yes vs. no)	5.810 (1.123–30.059)	0.036
Severe disease flare (yes vs. no)	5.198 (1.268–21.305)	0.022

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval.

formed and thromboprophylaxis was rarely used; around 20% of the patients received tests related to thrombosis screening and less than 1% of the patients received prophylaxis. Severe disease flare was an independent risk factor for venous thrombosis among hospitalized IBD patients.

IBD is an independent risk factor for venous thrombosis, and IBD patients had 2- to 4-fold risk of venous thrombosis compared to the general population.[3,4,16] Combined incidence for DVT and PE among IBD in Denmark and Canada ranged from 24 to 45.6 per 10,000 person-years.[1,3,4] Asian population had lower incidence of venous thrombosis compared to the Western population.[8] In recent years, 2 population-based

studies demonstrated 2-fold risks for venous thrombosis among IBD patients in East-Asia, similar to the Western population.[11,12] However, the actual incidence of venous thrombosis in these 2 studies ranged from 6 to 9.81 per 10,000 person-years,[11,12,17] with lower proportion of patients (0.79%–1.31%) with venous thrombosis compared to the Western population (3%–4%). The proportion of patients with venous thrombosis in the current study was similar to previous reports from Asia. Given such low proportion of patients with venous thrombosis, the high incidence was more likely to be overrated due to the relatively short follow-up time of the recruited patients, instead of selection bias as a result of potentially more severe disease presentations among patients that were enrolled from tertiary hospitals in the current study.

In addition to the incidence of venous thrombosis, we also reported that thrombosis screening and use of prophylaxis were relatively rare among IBD patients in Asia. Thromboprophylaxis was not considered a regular practice for over half of IBD physicians in Asia.[10] The actual use of thromboprophylaxis might be lower; we discovered that less than 1% of patients received thromboprophylaxis, which is similar to a report from Singapore in which none of the 152 hospitalized IBD patients received thromboprophylaxis.[17] Lower incidence of venous thrombosis results in less commonly practiced thromboprophylaxis compared to the West; however, close attention is needed for patients with high risk.[18] For the general population, older patients are among the high-risk groups for venous thrombosis.[8] In the current study, we discovered that risk for venous thrombosis also increased with age, and hospitalizations were longer among older patients. As aging becomes prevalent among the growing IBD population, venous thrombosis could be an emerging complication causing considerable mortality and impaired quality-adjusted life-years.[6] Therefore, standardized protocols for thromboprophylaxis for IBD patients in Asia are necessary, especially for patients with additional risks for venous thrombosis.[18] Many factors influence the cost-effectiveness of thromboprophylaxis, including incidence of venous thrombosis, the benefits of prophylaxis against risk of bleeding in different patient subgroups, and also socio-economic factors such as cost and compliance.[19,20] For patients in Asia, due to lower incidence of venous thrombosis in general and different socio-economic backgrounds, precise risk stratification models are needed. This would require incidence and risk factor studies among different patient subgroups, and also investigations into risk and benefits of thromboprophylaxis among Asian IBD patients.

Though thromboprophylaxis may not be a routine practice in the context of low incidence of venous thrombosis, screening and close monitoring are still necessary since IBD patients had 2-fold risk for venous thrombosis.[11,12] However, we discovered that use of thrombosis screening was relatively rare. Two previous studies from Japan showed much higher rates, ranging between 3.6% to 27.2%, for venous thrombosis with the use of proactive screening. Surprisingly, more than 50% of the reported thrombotic events were asymptomatic.[21,22] Therefore, proactive screening could be useful for early identification of thrombosis; this is especially important for thrombosis with atypical presentation such as intra-abdominal thrombosis. In our study, more patients developed intra-abdominal venous thrombosis than PE, and the reported symptoms were mostly nonspecific such as abdominal pain. Intra-abdominal thrombosis are common, especially for UC patients after surgery; recanalization is usually required to prevent deadly bowel ischemia and recurrent thrombosis.[23] Symptoms of intra-abdominal thrombosis are highly variable and could be confounded by IBD disease flare per se, causing delay in diagnosis and treatment. Therefore, screening for thrombotic events is crucial as it may avoid treatment delay if venous thrombosis truly develops.

Evidence regarding the appropriate choice of screening methods for IBD patients in Asia is limited. In the current study, the modality of screening was mainly D-dimer tests, with less than 3% of patients receiving ultrasound screening or computed tomography scans. A recent study showed elevated D-dimer at admission was highly predictive for venous thrombosis and therefore D-dimer test might be a useful screening tool.[24] However, another study suggested that the utility of D-dimer tests as screening methods could be limited, since elevated D-dimer is common in inflammatory diseases. Therefore, though D-dimer test is economical for initial screening, direct imaging study might be more appropriate for patients with high risks.[25] Further investigation into cost-effectiveness of screening methods are needed, especially for patients with high risk, such as patients during disease flares and patients undergoing surgery.

Several risk factors for venous thrombosis among hospitalized IBD patients have been previously reported, including disease flares, extensive disease, surgeries, use of steroids, and even hospitalization per se.[6,18,26-30] Similar to those previously reported, we discovered that severe disease flare was an independent risk factor for venous thrombosis. Elevated risks of venous thrombosis were reported among many autoimmune

diseases as a result of inflammation;[7,31,32] IBD patients during disease flares had 8-fold risks of venous thrombosis.[1,2,16,33] Most of patients in the our case-control study had active disease, possibly due to selection bias since patients were usually hospitalized due to flares. However, we showed that a more severely-active disease still exposed patients to higher risk for venous thrombosis. In addition, extensive gastrointestinal involvement exposed patients to higher risk of venous thrombosis, which was consistent with previous discoveries that pancolitis was associated with increased risk of venous thrombosis among UC patients.[12,16,28,30] These preliminary findings provided identifiable factors for risk stratification among hospitalized patients. Patients with these risk factors might be candidates to more proactive screening and prophylaxis.

The current study has several limitations. First, unlike previous population-based studies, relative risk of venous thrombosis for IBD patients was not analyzed due to lack of health data registry of the Chinese population in general. Second, due to limited access to resources as a retrospective multi-center study, only patients from tertiary referral hospitals were included, causing potential selection bias; in addition, hospitalized and ambulatory patients were not separately assessed. Therefore, we were not able to directly compare incidence and risk factors of venous thrombosis among different patient groups. Lack of such analysis limited the generalizability of the results, and therefore results of this study should only be applied to patients from tertiary referral hospitals. Future studies investigating venous thrombosis risk among different subgroups, such as patients being recently discharged, or postoperative patients, would provide evidence for more precise risk stratification strategies.

In conclusion, this study included a large number of IBD patients from tertiary referral hospitals as a representative of the Asian population and demonstrated a relatively low rate of venous thrombosis compared to the Western population. Thrombosis screening was only performed in a small proportion of patients, and prophylaxis was rarely practiced. Severely-active disease was a risk factor for hospitalized patients. Based on these findings, we suggested that thromboprophylaxis should be administered with caution given the lower likelihood of venous thrombosis. We also recommended that thrombosis screening could be valuable in avoiding treatment delay, especially for patients at high risks. Lastly, future studies are needed to explore risk stratification strategies for IBD patients in Asia, and also to evaluate the cost-effectiveness of thromboprophylaxis.

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