Original Article

Thromboembolic Events in Patients with Inflammatory Bowel Disease

Farjah H. Algahtani, Youssef M. K. Farag[1], Abdulrahman M. Aljebreen[2], Nahla A. Alazzam[2], Aamer S. Aleem, Fouad F. Jabri[3], Mohammad H. Rajab[3], Mohamed M. Shoukri[3]

Department of Medicine, Division of Hematology/Oncology, King Saud University College of Medicine and King Khalid University Hospital, [2]Gastroenterology Division, King Saud University College of Medicine, [3]AlFaisal University College of Medicine, Riyadh, Saudi Arabia, [1]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Address for correspondence:
Dr. Farjah H. Algahtani,
Hematology Consultant,
King Saud University, Riyadh,
Kingdom of Saudi Arabia.
E-mail: falgahtani@ksu.edu.sa

ABSTRACT

Background/Aims: Inflammatory bowel disease (ulcerative colitis and Crohn's disease) is characterized by a chronic inflammatory condition, and is accompanied by abnormalities in coagulation and a hyper-coagulable state. This study was conducted to examine the risk factors for developing Thromboembolic Events in Inflammatory Bowel Disease (IBD) in a population with prevalent consanguinity. **Patients and Methods:** Patients with a definitive diagnosis of IBD who were seen in the gastroenterology clinic of King Khalid University Hospital (Riyadh, Saudi Arabia) from 2010- to 2012, were asked to participate in this prospective cohort study, and were followed for one 1 year. Data was collected using specifically designed case report forms (CRF) by trained research personnel. **Results:** A total of 100 Saudi patients with IBD were studied. There were 51 (51%) women and the mean ± standard deviation (SD) age of the group was 31.24 ± 10.78 years. Those with Crohn's disease constituted 72% of the patients, and 28% had ulcerative colitis. Eight patients (8%) had at least one Thrombotic Event ([six deep venous thrombosis (DVT), and two pulmonary embolism (PE)]. Family history of deep venous thrombosis was present in 5%, and family history of pulmonary embolism (PE) in 4% of the patients. After adjusting for age and gender, a family history of Thrombotic event was identified as to be the only statistically significant predictor of thrombosis in IBD patients (RR = 9.22, 95% CI: 2.10--40.43). **Conclusion:** In a population with high consanguinity, Thromboembolic events (DVT and PE) had a prevalence of 8% among IBD patients, positive family history of pulmonary embolism was a predictor of thrombosis. Further studies are needed to explore the role of genetic factors in this population.

Key Words: Deep vein thrombosis, inflammatory bowel disease, pulmonary embolism, thromboembolism, thrombosis, thrombosis, venous thromboembolism

Inflammatory bowel disease (IBD) is a group of digestive system diseases comprising of ulcerative colitis (UC) and Crohn's disease (CD), whose etiology is not completely elucidated.[1,2] IBD is characterized by a chronic inflammatory condition, and is accompanied by abnormalities in coagulation and a hypercoagulable state.[3]

The risk of Thromboembolism Events (TEE) in IBD is 3--4 fold more than that in the general population.[4] The reported prevalence of TEE in IBD ranges between 1.2% and 6.1% and has been shown to be up to 39% in some necropsy studies.[5-9] TEE is a serious complication of IBD occurring in a relatively younger patient population, with the most common site being the deep veins of the leg, pulmonary vessels; and other reported sites including cerebral, hepatic, and mesenteric vessels.[10,11]

The extent of colonic disease has a correlation with thromboembolic risk. Extensive ulcerative colitis and colonic involvement in Crohn's disease were significantly associated with the development of thromboembolism.[12] An English study reported an 8.4 times higher risk of venous TEE in IBD patients with increased disease activity as compared to controls.[13]

Several acquired thrombotic risk factors may be present in IBD including the inflammatory process *per se*, prolonged immobilization, use of corticosteroids, surgical treatment, fluid depletion, central venous catheters, hyperhomocysteinemia, smoking, and use of oral contraceptives.[14] Over half of the cases of VTE in IBD may be associated with factor V Leiden and prothrombin gene mutation,[15], which may indicate that genetic factors play a role in TEE, however, this is inconsistent with other studies.[16] The exact mechanism of thrombosis in IBD remains controversial. Reported coagulation abnormalities in IBD include activation of the markers of coagulation, disturbed fibrinolysis, and activation of platelets.[17] In addition, activated protein C (APC) resistance was found in approximately 30% of patients with IBD and TEE.[18] This study was conducted to examine the risk factors for developing thromboembolic events in an IBD population with prevalent consanguinity.

PATIENTS AND METHODS

Study population
To avoid selection bias, consecutive patients with definitive diagnosis of IBD (UC or CD) who were seen at the gastroenterology clinics of King Khalid University Hospital (Riyadh, Saudi Arabia), were asked to participate in this study conducted during 2010-–2012. The study was approved by the institutional review board (NO.09-703), informed consent was obtained from those who agreed to be enrolled in the study, the data was collected. Definitive diagnosis of IBD was considered radiological, endoscopic, and histological workup. Endoscopic evaluation was repeated at the time of the study enrollment for confirmation of the extent of disease for all patients.

Exclusion criteria included being on specific medication categories, e.g., oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and contraceptives as these medications may have caused platelet or coagulation abnormalities during the previous 8 weeks before blood sampling. Patients were also excluded if they had impaired renal or liver function, a myeloproliferative disorder, or cancer during enrollment period. None of the patients in the IBD group had any previous thrombotic episode.

Data collection
Demographic data of all participants such as age, gender, types of IBD, extent of disease, family history of thromboembolic events (TEE), common risk factors for TEE, and type/site of vascular complication, were collected. No information on the severity of IBD was collected. Blood samples were collected to perform study-related laboratory analyses on any patient who developed symptoms of DVT and/or PE, were objectively confirmed by compression ultrasound or venography and by spiral computed tomography or ventilation/perfusion lung scanning, respectively.

Laboratory methods
Blood samples were taken for laboratory workup complete blood count (CBC). liver function tests (LFT), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Venous blood was collected into 0.129 ml trisodium citrate (1:10), and the plasma samples were stored at −80°C, then processed for activated partial thromboplastin time (PT), international normalized ratio (INR), protein C, protein S Ac, antithrombin III (A), FVL (ProC Global, Dade Behring, USA), lupus anticoagulant (LA1 Screening Reagent/LA2 Confirmation Reagent, Dade Behring, USA), and anticardiolipin antibody (ACA) IgG and IgM (Dade Behring, USA).

All laboratory analyses were performed in the hospital's laboratory which was standardized and certified by Accreditation Canada.

Statistical analysis
Data were collected in a specially-designed case report form (CRF) and manually entered in the Microsoft Excel spreadsheet. All statistical analyses were performed using Stata Software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: Stata Corp LP). Continuous variables were summarized using means and standard deviation, and categorical variables were summarized using frequency numbers and percentage distributions. Comparison of variables' summary statistics across groups were performed using student's *t*-test to compare means of continuous variables. We also performed normality testing for continuous variables using the nonparametric Kolmogorov–Smirnov test (K–S test). If the tested variable was found to be abnormally distributed, Mann–Whitney U test was used.

To compare the categorical variables' summary statistics across groups, we used Chi-square test. If at least one of the cells in any of the contingency table contained expected count of <5, Fisher's exact test was used instead.

To identify the predictors of thrombosis in IBD patients, we developed two models using the log-binomial regression analysis and calculated unadjusted and adjusted relative

risks. The adjusted model included age and gender as confounding variables. The results of the log-binomial regression were represented as relative risk of developing the outcome (thrombosis) in patients who had the exposure variable, compared to those who did not have the exposure. We manually created models for each exposure variable, and because of very low prevalence of many of the exposure variables, the relative risks were not calculated, and hence omitted from the tables in this manuscript. Subgroup regression analysis by IBD category was not performed due to the small count of each individual category. The 95% confidence intervals were also calculated for each predictor. A probability below 0.05 was considered to be statistically significant for all tests.

RESULTS

Overall study population
A total of 100 Saudi patients with IBD were followed with a mean (±SD) age of 31.24 ± 10.78 years, 51 (51%) women. Seventy-two (72%) patients had CD and twenty eight (28%) had UC. Eight patients (8%) had at least one

thrombotic event (six DVT, and two PE). Twenty percent of the patients had a history of surgery in the past, 5% had a family history of deep venous thrombosis (DVT) and 4% had a family history of pulmonary embolism (PE). Other characteristics of the study population are presented in Table 1. None of the patients had concomitant DVT and PE or other complications.

Differences among thrombotic and non-thrombotic IBD inflammatory bowel disease patients
All thrombotic events in 8 patients occurred exclusively with Crohn's Disease ($P = 0.07$).

Non-thrombotic and thrombotic IBD patients were similar in age (31.25 ± 10.79 vs. 31.13 ± 11.36 years, $P = 0.98$), and family history of DVT (4.35% vs. 12.50%, $P = 0.31$). However, patients with thrombosis had a statistically significant family history of PE (2.17% vs. 25%, $P = 0.002$). None of the laboratory variables were found to be statistically significant across the thrombotic and non-thrombotic IBD patients. Detailed comparisons between the two groups are given in Table 1.

Table 1: Baseline demographic and clinical characteristics of IBD patients according to thrombosis status			
	Total study participants	Patients without thrombosis	Patients with thrombosis	P-value
Age, years	31.24±10.78	31.25±10.79	31.13±11.36	0.98
Gender				0.43
Male	49 (49%)	48 (52.17%)	3 (37.50%)	
Female	51 (51%)	44 (47.83%)	5 (62.50%)	
Diagnosis				0.07
CD	72 (72%)	64 (69.57%)	8 (100%)	
UC	28 (28%)	28 (30.43%)	0 (0.00%)	
Family history of DVT	5 (5%)	4 (4.35%)	1 (12.50%)	0.31
Family history of PE	4 (4%)	2 (2.17%)	2 (25.00%)	0.002*
Abortion	5 (5%)	4 (4.35%)	1 (12.50%)	0.31
Miscarriage	5 (5%)	5 (5.43%)	0 (0.00%)	0.5
Heart failure	1 (1%)	1 (1.09%)	0 (0.00%)	0.77
Nephrotic syndrome	1 (1%)	1 (1.09%)	0 (0.00%)	0.77
Surgery	20 (20%)	20 (21.74%)	0 (0.00%)	0.14
Postpartum hemorrhage	8 (8%)	7 (7.61%)	1 (12.50%)	0.63
H/O oral contraceptive pill	4 (4)	3 (3.26%)	1 (12.50%)	0.20
Thrombosis	8 (8%)	0 (0.00%)	8 (100%)	0.00
WBC count, ×10⁹ per liter (L)	6.94±2.38	6.76±2.31	8.94±2.35	0.01*
Hemoglobin, g/L	129.41±18.26	129.88±18.42	124.25±16.5	0.40
Platelet count, ×10⁹/L	323.79±125.06	322.92±126.41	333.5±116.13	0.82
C-Reactive Protein, mg/L	16.72±24.87	17.47±25.59	6.11±2.53	0.45
Fibrinogen, g/L	3.83±1.02	3.86±1.01	3.61±1.17	0.51
Prothrombin time (PT), seconds	14.68±0.99	14.66±0.99	14.88±1.10	0.64
Activated Partial Thromboplastin Time (APTT), seconds	38.28±4.92	38.46±3.88	36.78±11.00	0.48
Thrombin Time (TT), seconds	18.09±1.39	18.00±1.38	18.85±1.36	0.10
D-Dimer, mcg/mL fibrinogen equivalent units: FEU	0.52±0.49	0.52±0.49	0.56±0.58	0.84
Serum albumin	36.24±5.35	36.24±5.21	36.25±6.86	0.99
Urea	3.93±1.5	3.91±1.53	4.08±1.25	0.77
Serum creatinine	65.25±18.90	65.03±19.37	67.25±14.77	0.75

Predictors of thrombosis in inflammatory bowel disease

In the crude regression model, predictors of thrombosis in IBD patients were identified as female gender (RR = 1.73, 95% CI: 0.44-–6.87), a family history of DVT (RR = 2.71, 95% CI: 0.41-–18.01), and a family history of PE (RR = 8.00, 95% CI: 2.29-–27.90). After adjusting for age and gender, only the family history of PE retained statistical significance (RR = 9.22, 95% CI: 2.10-–40.43), [Table 2].

DISCUSSION

This study showed the prevalence of thrombosis to be 8% in this cohort of IBD patients. We also found that a family history of PE was a significant predictor of thrombosis in IBD patients with approximately 9 times higher risk of developing thrombosis when compared to those with a negative family history of PE. The reported prevalence of thrombosis in IBD patients has varied in different studies. In Tunisia, the prevalence of thromboembolic complications was found to be 3.4% in patients with IBD.[19] In another cohort study, the prevalence and incidence rate of all VTE was 5.6% and 6.3 per 1000 person years, respectively. Patients with VTE were older at IBD diagnosis than those without VTE (34.4 ± 14.8 years vs. 32.1 ± 14.4 years, P = 0.045), but however, did not differ by gender.[20] Nevertheless, we did not find any difference in age between thrombotic and non-thrombotic IBD patients. An epidemiological review demonstrated that IBD patients had a 1.5- to 3.5-fold higher risk of incurring VTE when compared with non-IBD patients and IBD activity was an independent risk factor for VTE development.[21]

Disease activity and genetic predisposition have been considered to be predictors of thromboembolic events in IBD patients. Suárez Ferrer *et al.* showed that more extensive involvement and severe inflammatory activity were risk factors for thrombosis in IBD patients and no significant association between classical risk factors such as the use of contraceptives, pregnancy, coagulation disorders or smoking, and the risk of thromboembolic phenomena were found.[22] These results are similar to our study; however, unlike our finding, none of their patients had a family history of thrombosis. Regarding the genetic factor in IBD, one study found that increased prevalence of hyperhomocysteinemia in IBD patients might account for the thrombotic risk.[23] Although another study reported the same finding, they found that there was no correlation between hyperhomocysteinemia and a history of prior thromboembolic event.[24] The investigators in the two studies concluded that in patients with IBD, inheritance of a specific gene mutation results in a significant increased risk of venous thrombosis.[25,26] This was contradicted by another study.[27] Although we did not present genetic analysis here, these studies may explain our results that a family history of thrombosis increases the risk of thromboembolic events. Such association in our study could possibly be attributed to the high prevalence of consanguinity in the community. However, this variable was not asked in the CRF.

It is interesting to note that all our patients with TEE had underlying CD. It is difficult to explain but appears to be by chance as most of the previous studies have not shown any significant difference in the prevalence of thrombosis between CD and UC.[28]

This study has certain limitations. A small sample size, which possibly yielded weak associations with many of the exposure variables and may limit generalization of the results.

Another limitation of our study is the lack of complete genetic analysis. However, the strong association between the family history of PE and thrombosis in IBD patients indicate the importance of genetic factors in the pathogenesis of thrombosis in this group of patients. Further studies are needed and research should be encouraged to explore the role of genetic markers in this area.

Conflicts of interest
There are no conflicts of interest.

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Table 2: Regression analysis to identify risk factors and predictors for thrombosis in IBD patients, presented as relative risks (RR), and 95% confidence intervals (95% CI)

	Crude model	Age-and gender-adjusted model
Gender		
Male	1.00 (reference)	1.00 (reference)
Female	1.73 (0.44-–6.87)	1.74 (0.44-–6.96)
Family history of DVT		
No	1.00 (reference)	1.00 (reference)
Yes	2.71 (0.41-–18.01)	2.44 (0.32-–18.36)
Family history of PE		
No	1.00 (reference)	1.00 (reference)
Yes	8.00 (2.29-–27.90)	9.22 (2.10-–40.43)

426
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