

Inflammatory bowel disease and thromboembolic events: a c'lot to learn

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Abstract

Background: Inflammatory bowel disease (IBD) is associated with a variety of extraintestinal manifestations including arterial and venous thromboembolism. Research evidences that IBD patients have about a 2- to 3-fold increase in the risk of venous thromboembolism when compared with the general population.

Objectives: We intended to evaluate the coagulation parameters and the prevalence of thromboembolic events (TE) in IBD patients. It was also our aim to investigate the correlation between coagulation parameters and disease phenotype and activity in this population.

Methods: This single center prospective observational study was performed between November 2016 and April 2020. The cohort included patients with 18 years of age or older, diagnosed with IBD and followed at a gastroenterology consultation, during a follow-up period of 36 months. Patients were evaluated in terms of IBD type, extent and disease behavior, clinical scores of IBD activity, medication, smoking history, family and personal history of TE, coagulation parameters, fecal calprotectin levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hospitalization due to TE, IBD-related hospitalization or surgery, pregnancy, or diagnosis of malignancy.

Results: The study included 149 IBD patients (67 males and 82 females). Coagulation parameters were similar in CD and UC patients and only plasminogen was increased in CD patients [97.4 (17.0) *versus* 91.6 (13.3), $p=0.035$], when comparing with UC patients. The determined values were in the range of the reference values described in literature for the standard population. During the follow-up period, none of the patients experienced a TE that demanded hospitalization.

Conclusion: In our study, acquired and inherited risk factors for TE and changes in coagulation parameters did not show to influence prothrombotic predisposition in IBD patients. As such, the clinical relevance of measuring coagulation parameters in this population is questionable.

Trial Registry: NCT05162339 (ClinicalTrials.gov ID).

Keywords: coagulation parameters, genetic background, inflammatory bowel disease, risk factors, thromboembolic events

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Introduction

Inflammatory bowel disease (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), is a group of systemic disorders associated with chronic, recurrent, and immune system-mediated inflammation of the bowel mucosa, that predominantly affect the gastrointestinal tract, but are also

associated with a number of extraintestinal manifestations.^{1,2}

IBD is a known risk factor for arterial and venous thromboembolism,^{3,4} which are often life-threatening complications and an important cause of morbidity and mortality in these patients.^{4–6} The

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reported prevalence of thromboembolic events (TEs) in IBD patients ranges between 1% and 8%.^{5,7} Deep vein thrombosis and pulmonary embolism are the most frequently described TE in IBD. Nevertheless, retinal veins, mesenteric veins, portal veins, and arteries can also be affected.^{6,8}

Compared with the healthy population, IBD patients have about a 2- to 3-fold increase in the risk of venous thromboembolism^{3,9-11} and are affected at a young age.¹²⁻¹⁴ In addition, up to 30% of IBD patients also have a higher likelihood (about 2.5-fold) of recurrent TE compared with patients without IBD.^{6,12} In addition, the presence of active disease has been shown to increase the likelihood of TE among patients with IBD, with a 16-fold risk increase during a disease flare.^{5,9,15,16} Disease extent was also associated with increased odds of TE. In fact, the risk was shown to be higher in patients with pancolitis in UC and with ileocolonic involvement in CD, especially in patients with strictures, abscess, or fistula.^{1,13} The incidence of these events also seems to be correlated to hospitalization, surgery, pregnancy, and puerperium with a 2-fold higher risk, and the use of corticosteroids and oral contraceptives.^{14,16}

The mechanism underpinning increased thrombotic propensity in IBD is not fully understood.⁶ However, research seems to indicate that it is a multifactorial event related to disease activity and inflammatory state, involving the coexistence of inherited and acquired risk factors that multiply the prothrombotic risk.^{5,9} In patients with active disease, intestinal inflammation causes a prothrombotic state that, in association with immobility due to severe illness, malnutrition, and surgical requirements, results in a higher predisposition to TE.^{3,5,9}

Despite the incidence of TE in IBD patients, the impact of this condition on coagulation mechanisms has not been studied. The aim of this study was to characterize the coagulation parameters in a sample of IBD patients and to determine the prevalence and risk factors for TE during a follow-up period of 36 months. We also intend to investigate the correlation between variations in the coagulation parameters and disease phenotype and activity.

Materials and methods

Study design and patient selection

This single-center prospective observational study was performed between November 2016 and April 2020. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies.¹⁷

We included patients who were 18 years of age or older, diagnosed with IBD (ECCO criteria), and followed up at an IBD consultation at Centro Hospitalar Tondela-Viseu, between November 2016 and April 2017. Patients were randomly selected to participate in the study, and informed consent to treatment was obtained. At the entrance, all patients had their clinical data collected; blood and stool samples were taken for routine evaluation and study of coagulation factors (Figure 1). The study included an IBD consultation at least twice a year, during a follow-up period of 36 months, to evaluate disease phenotype and activity, and assess the occurrence of hospitalization due to TE.

Individuals with other risk factors for TE like severe hepatic or renal failure, valvular heart disease, atrial fibrillation, heart failure or cardiomyopathy, pregnancy, and oral anticoagulants or heparin at study entry were excluded.

Data collection

TE was defined as deep vein thrombosis, pulmonary embolism, mesenteric vein thrombosis, or portal vein thrombosis; superficial thrombophlebitis was excluded from the definition.

Data collection included age, sex, body mass index (BMI), IBD type (Crohn's disease, ulcerative colitis), age at diagnosis of IBD, extent and disease behavior, clinical scores of IBD activity (Harvey-Bradshaw score, partial Mayo score), IBD medication exposure, anticoagulation exposure, hormone replacement therapy, smoking history, comorbidities (including cardiovascular comorbidities such as high blood pressure, high cholesterol or triglycerides levels, diabetes and obesity), surgical intervention in the last 3 months, family and personal history of TE, platelet count, V factor, VIII factor, VII factor,

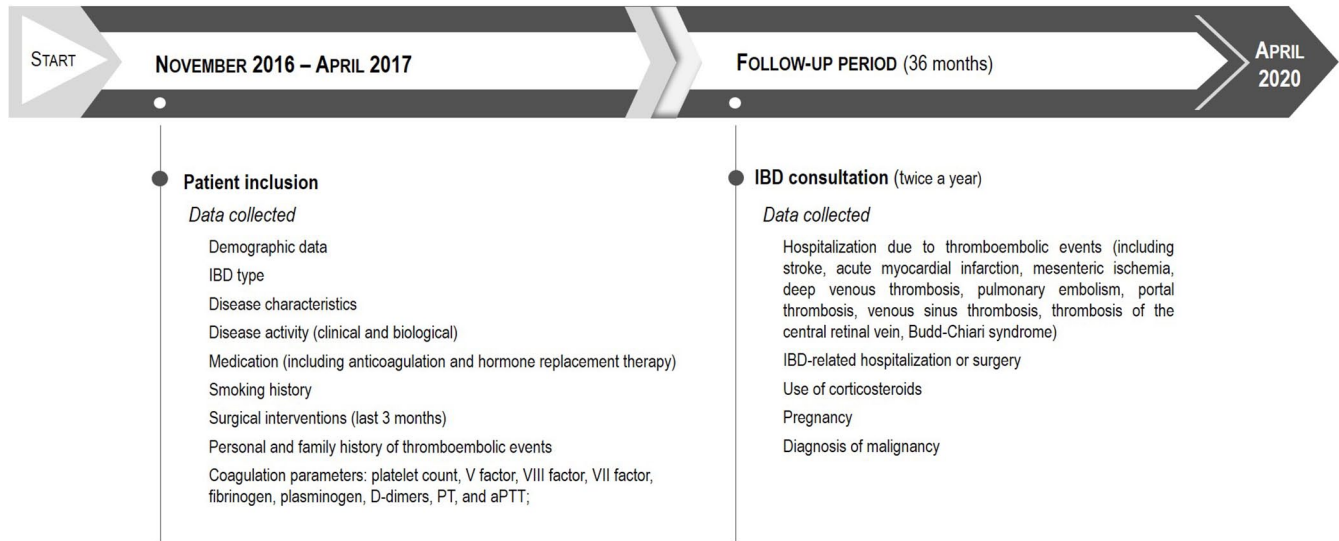


Figure 1. Study timeline and data collected.

fibrinogen, plasminogen, D-dimers, prothrombin time (PT), activated partial thromboplastin time (aPTT), fecal calprotectin levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hospitalization due to TE (stroke, acute myocardial infarction, mesenteric ischemia, deep venous thrombosis, pulmonary embolism, portal thrombosis, venous sinus thrombosis, thrombosis of the central retinal vein, Budd–Chiari syndrome), IBD-related hospitalization or surgery (it was also documented if TE prophylaxis was administered throughout hospital stay), use of oral corticosteroids, pregnancy or diagnosis of malignancy (Figure 1). All patients' details were de-identified.

Statistical analysis

The collected data was analyzed by the SPSS (Statistical Package for Social Sciences®). Descriptive statistics were used for patient demographics and disease characteristics. Categorical variables are given as proportions or absolute counts, and comparisons were made with Pearson's χ^2 test and Fisher test. Continuous data are expressed as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for nonnormally distributed data; comparisons were performed with Student's *t*-test and ANOVA tests, or Mann–Whitney *U* and Kruskal–Wallis tests. Results were reported as HRs with a 95% confidence interval.

Ethical considerations

The study was approved by the local ethics committee (Ethics Committee of Centro Hospitalar Tondela-Viseu, E.P.E, in September 2016) and conducted according to the Declaration of Helsinki.

Results

Between November 2016 and April 2017, 162 patients with IBD were identified. Thirteen patients were excluded due to atrial fibrillation and need for oral anticoagulation medication ($n=7$), renal failure ($n=4$) and pregnancy at study entry ($n=2$), leaving 149 patients for further analysis.

Clinical data upon baseline evaluation of the patients enrolled in this prospective observational study are described in Table 1. The study included 49 (20 males and 29 females) patients with UC (32.9%) and 100 (47 males and 53 females) patients with CD (67.1%). The mean ages at baseline were 45.1 (15.2) years for UC patients and 41.0 (14.5) years for CD patients, with no significant difference ($p=0.112$). Gender distribution and mean disease duration (9.0 (8.2) years *versus* 8.2 (6.9) years, $p=0.527$) were also similar between patients with UC and CD, respectively.

At least one cardiovascular comorbidity was found in 20.8% of patients with IBD. The rate of

Table 1. Baseline characteristics of the study population.

Characteristics	Ulcerative colitis (n=49)	Crohn's disease (n=100)	p value
Age, mean (SD), years	45.1 (15.2)	41.0 (14.5)	0.112 ^a
Sex, n (%)			
Female	29 (59.2)	53 (53.0)	0.476 ^b
Male	20 (40.8)	47 (47.0)	
Comorbidities, n (%)			
Yes	13 (26.5)	18 (18.0)	0.228 ^{b,1}
Cardiovascular	13 (26.5)	15 (15.0)	
Non cardiovascular	0 (0)	3 (3.0)	
No	36 (73.5)	82 (82.0)	
BMI, mean (SD), kg/m ²	23.1 (4.6)	23.2 (4.8)	0.842 ^a
Smoking history, n (%)			
Current	1 (2.0)	23 (23.0)	0.001^b
Past	7 (14.3)	22 (22.0)	
Never	41 (83.7)	55 (55.0)	
Hormonal therapy, n (%)			
Yes	7 (14.3)	11 (11.0)	0.563 ^b
No	42 (85.7)	89 (89.0)	
Prior history of TE, n (%)			
Yes	1 (2.0)	5 (5.0)	0.664 ^{c,2}
Stroke	0 (0)	2 (2.0)	
Acute myocardial infarction	1 (2.0)	0 (0)	
Deep venous thrombosis	0 (0)	1 (1.0)	
Venous sinus thrombosis	0 (0)	1 (1.0)	
Pulmonary thromboembolism	0 (0)	1 (1.0)	
No	48 (98.0)	95 (95)	
Family history of TE, n (%)			
Yes	17 (34.7)	44 (44.0)	0.278 ^{b,3}
Stroke	14 (28.6)	29 (29.0)	
Acute myocardial infarction	2 (4.1)	9 (9.0)	
Deep venous thrombosis	1 (2.0)	6 (6.0)	
No	32 (65.3)	56 (56.0)	

BMI, body mass index; SD, standard deviation; TE, thromboembolic event.

^aStudent's *t*-test; ^bChi-square test; ^cFisher's test.

¹*p* value relative to the comparison of the groups 'with comorbidities' and 'without comorbidities'.

²*p* value relative to the comparison of the groups 'with prior history of TE' and 'without prior history of TE'.

³*p* value relative to the comparison of the groups 'with family history of TE events' and 'without family history of TE events'.

tobacco smokers was higher among patients with CD (23.0%) than in those with UC (2.0%) ($p=0.001$). Only 12.1% of patients were on hormonal therapy (oral contraceptives), with no significant difference between UC and CD patients (14.3% *versus* 11.0%, $p=0.563$).

Six patients (4.0%) had a prior history of TE, namely one patient with UC had an acute myocardial infarction and five patients with CD had two strokes, one acute MI, DVT, venous sinus thrombosis, and PTE, with no significant difference between both groups ($p=0.664$). Regarding the family history, about 41% of patients had at least one family member with a prior TE (44.0% of patients with CD and 34.7% of patients with UC); stroke was the most frequent occurrence in both groups (29.0% in CD patients and 28.6% in UC patients), with no significant difference ($p=0.278$) between both groups.

Table 2 represents baseline characteristics of the study population regarding IBD.

In CD, ileal disease was found in 42 (42.0%) patients, colonic in 14 (14.0%), and ileocolonic in 44 (44.0%). The results showed involvement of the upper GI tract in 8 patients (8.0%), and perianal disease in 30 (30.0%) patients with CD. Disease behavior was nonstricturing/nonpenetrating in 29 (29.0%) patients, stricturing in 31 (31.0%) patients, and penetrating in 40 (40%) patients. Among the 49 patients with UC, 27 (55.1%) had pancolitis, 15 (30.6%) had left-sided colitis, and 7 (14.3%) had proctitis.

A higher number of CD patients (44.0%) had already undergone bowel surgery compared with those with UC (44.0% *versus* 8.2%, $p<0.001$); only three CD patients had been submitted to a recent surgical procedure.

Regarding extraintestinal manifestations, data was similar in both groups (28.6% of UC, 21.0% of CD, $p=0.306$), but current therapy for IBD was significantly different between UC and CD patients ($p<0.001$).

Concerning IBD activity scores (partial Mayo Score in UC and Harvey–Bradshaw in CD), most patients were in clinical remission (57.1% with UC and 65.0% with CD). Regarding inflammatory parameters, median calprotectin levels were

statistically different in UC and CD patients [284.00 (1264.50) $\mu\text{g/g}$ in UC *versus* 129.00 (390.25) $\mu\text{g/g}$ in CD, $p<0.05$].

The results regarding coagulation parameters are described in Table 3. The groups showed similar results, although mean plasminogen levels were increased in CD patients [97.4 (17.0)% *versus* 91.6 (13.3)%, $p=0.035$], when compared with UC patients. The studied coagulation parameters were in the range of the reference values described in the literature for a standard population.

Supplemental Tables 1 and 2 summarize the influence of IBD-related variables on coagulation parameters. Regarding CD (Supplemental Table 1), patients aged 30 years or older, at the time of diagnosis had significantly lower PT values [11.30 (0.94) s *versus* 11.78 (0.91) s, $p=0.011$], and increased D-dimer values [111.00 (77.25) ng/ml *versus* 78.50 (58.00) ng/ml, $p=0.006$], compared with patients younger than 30 years. Disease location, disease behavior, and the presence of perianal disease or extraintestinal manifestations did not significantly influence any of the evaluated coagulation parameters. However, patients with upper GI tract involvement seem to have lower PT values [10.90 (0.58) s *versus* 11.62 (0.96) s, $p=0.0399$].

Regarding patients who underwent IBD-related surgery, fibrinogen values were significantly lower [3.65 (1.70) g/dl *versus* 4.15 (2.05) g/dl, $p=0.037$] and Factor VIII levels were increased [151.18 (16.29)% *versus* 111.00 (4.58)%, $p=0.016$], in CD.

At baseline, inpatients with CD had significantly higher D-dimer values [246.00 (219.00) ng/ml *versus* 91.00 (61.00) ng/ml, $p=0.009$], whereas UC patients had significantly higher PT values [12.95 (0.64) s *versus* 11.65 (0.12) s, $p=0.005$], compared with outpatients.

In CD patients, smoking history and BMI did not seem to influence coagulation parameters, but the use of oral contraceptives was associated with increased levels of Factor VII [105.25 (8.21)% *versus* 87.81 (2.82)%, $p=0.043$]. However, in the UC population, smoking habits and oral contraceptives did not seem to play a significant role in influencing coagulation parameters, but a BMI ≥ 25 kg/m² relates to higher values of PT [12.23 (0.26) s *versus* 11.57 (0.14) s, $p=0.019$].

Table 2. Baseline characteristics of the study population regarding IBD.

Characteristics	Ulcerative colitis (n=49)	Crohn's disease (n=100)	p value
Age at diagnosis, mean (SD), years	35.9 (14.7)	32.8 (14.8)	0.222 ^a
Disease duration, mean (SD), years	9.0 (8.2)	8.2 (6.9)	0.527 ^a
Location, n (%)			
L1 (Ileal)	-	42 (42.0)	-
L2 (Colonic)		14 (14.0)	
L3 (Ileocolic)		44 (44.0)	
E1 (Ulcerative proctitis)	7 (14.3)	-	
E2 (Left-sided colitis)	15 (30.6)		
E3 (Extensive disease)	27 (55.1)		
Disease behavior, n (%)			
B1 (nonstricturing, nonpenetrating)	-	29 (29.0)	-
B2 (stricturing)		31 (31.0)	
B3 (penetrating)		40 (40.0)	
Perianal disease, n (%)			
Yes	-	30 (30.0)	-
No		70 (70.0)	
Upper GI tract involvement, n (%)			
Yes	-	8 (8.0)	-
No		92 (92.0)	
Extraintestinal manifestations, n (%)			
Yes	14 (28.6)	21 (21.0)	0.306 ^b
No	35 (71.4)	79 (79.0)	
Surgery IBD-related, n (%)			
Yes	4 (8.2)	44 (44.0)	<0.001 ^{c,1}
Last 3 months	0 (0)	3 (3.0)	
No	45 (91.8)	56 (56.0)	
Current therapy for IBD, n (%)			
Classic immunosuppressors [†]	9 (18.4)	18 (18.0)	<0.001 ^{b,2}
Biological therapy [‡]	18 (36.7)	65 (65.0)	
Aminosalicylates	20 (40.8)	9 (9.0)	

(Continued)

Table 2. (Continued)

Characteristics	Ulcerative colitis (n = 49)	Crohn's disease (n = 100)	p value
No therapy	2 (4.1)	8 (8.0)	
Hospitalization at baseline, n (%)			
Yes	4 (8.2)	3 (3.0)	0.218 ^c
No	45 (91.8)	97 (97.0)	
Harvey–Bradshaw score, n (%)			
0–4 (remission)	-	65 (65.0)	-
5–7 (mild disease)		18 (18.0)	
8–16 (moderate disease)		16 (16.0)	
>16 (severe disease)		1 (1.0)	
Partial Mayo score, n (%)			
0–1 (remission)	28 (57.1)	-	-
2–4 (mild disease)	10 (20.4)		
5–6 (moderate disease)	5 (10.2)		
7–9 (severe disease)	6 (12.2)		
CRP, median (IQR), mg/dl	0.2 (0.5)	0.3 (0.9)	0.452 ^d
ESR, median (IQR), ms	7.0 (13.5)	8.0 (11.0)	0.606 ^d
Calprotectin, median (IQR), µg/g	284.0 (1264.5)	129.0 (390.3)	0.019^d
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IBD, inflammatory bowel disease; IQR, interquartile range. ^a Student's <i>t</i> -test; ^b Chi-square test; ^c Fisher's test; ^d Mann–Whitney test. ¹ <i>p</i> value relative to the comparison of the groups 'surgery IBD-related' and 'no surgery IBD-related', with no statistical significance in the group of patients 'surgery IBD-related in the last 3 months' (<i>p</i> =0.551, by the Fisher's test). ² <i>p</i> value relative to the comparison of the four therapeutic groups. [†] Azathioprine, Mercaptopurine or Methotrexate in monotherapy. [‡] Biological therapy (Infliximab, Adalimumab, Vedolizumab or Ustekinumab) in monotherapy or in combination with classic immunosuppressive therapy.			

The presence of comorbidities led to increased values of D-dimer in CD patients [111.00 (147.50) ng/ml *versus* 88.00 (60.75) ng/ml, *p*=0.047] and to higher values of fibrinogen [4.50 (1.95) g/dl *versus* 3.60 (1.48) g/dl, *p*=0.008] and Factor VIII [131.84 (8.11)% *versus* 107.94 (5.26)%, *p*=0.021] in UC patients.

Prior history or family history of major TE did not seem to correlate with significant changes in coagulation parameters in either CD or UC.

Active IBD was associated with significant differences in the levels of D-dimer, fibrinogen, and Factor VIII. CD activity, based on the Harvey–Bradshaw clinical score, significantly influences D-dimer (*p*=0.039) and fibrinogen (*p*=0.043) levels, with higher values associated with moderate and severe disease, regarding D-dimers. Likewise, UC activity, based on the partial Mayo score, significantly influences D-dimer (*p*=0.043) and Factor VIII (0.019) levels, with higher values associated with moderate and severe disease.

Table 3. Coagulation parameters of the study population according to Ulcerative Colitis characteristics, at baseline.

Characteristics	Ulcerative colitis (n=49)	Crohn's disease (n=100)	p value
Platelets, mean (SD), ×10 ³ /L	228.90 (52.29)	249.28 (64.76)	0.057 ^a
PT, mean (SD), s	11.76 (0.90)	11.56 (0.95)	0.229 ^a
aPTT, median (IQR), s	29.80 (4.10)	29.70 (3.47)	0.700 ^b
D-dimer, median (IQR), ng/ml	107.00 (97.00)	93.00 (70.75)	0.129 ^b
Fibrinogen, median (IQR), g/dl	3.70 (1.80)	3.95 (2.10)	0.138 ^b
Plasminogen, mean (SD), %	91.55 (13.30)	97.40 (17.03)	0.035^a
Factor V, mean (SD), %	67.51 (34.49)	71.02 (35.18)	0.565 ^a
Factor VII, mean (SD), %	82.84 (22.59)	89.73 (27.06)	0.126 ^a
Factor VIII, mean (SD), %	114.28 (32.48)	127.11 (47.68)	0.091 ^a

aPTT, activated partial thromboplastin time; IQR, interquartile range; PT, prothrombin time; SD, standard deviation.
^aStudent's *t*-test; ^bMann-Whitney *U* test.

Table 4 describes the 36 months follow-up period that included biannual visits for the 149 included patients; none of these patients experienced a significant venous or arterial TE that needed hospitalization. During this period, 16.3% of UC patients were hospitalized, and 4.1% underwent bowel surgery related to IBD decompensation. As for CD patients, 28.0% required hospitalization and 18.0% underwent surgery for decompensation of their underlying intestinal disease. All patients hospitalized or submitted to surgery during follow-up were given enoxaparin in a prophylactic dose.

The use of oral corticosteroids related to IBD was similar in both groups (20.4% of UC patients and 17.0% of CD patients, *p*=0.612), and most patients required only 1 cycle of therapy during the considered follow-up period. None of the patients started JAK inhibitor therapy during follow-up.

More women with UC became pregnant during follow-up (13.8% with UC *versus* 1.9% with CD, *p*=0.05); pregnancy and postpartum were uneventful in both groups. No CD patients were diagnosed with cancer, as opposed to UC patients, with two deaths related to advanced lung and prostate cancer.

Discussion

In this prospective observational study, we characterized the coagulation parameters and determined the prevalence of TE during a follow-up period of 36 months in an IBD cohort. The obtained results demonstrated that the evaluated coagulation parameters were in the range of the reference values described in literature for the standard population and were similar in CD and UC subgroups. Furthermore, the registered changes and the identified risk factors do not increase the overall risk of TE.

The actual incidence of TE in IBD patients as an associated complication, is not known, but the prevalence seems to be higher in younger patients with active, extensive (pancolonic UC or CD with ileocolonic involvement) and complicated (strictures, fistulas, abscesses) disease.^{4,9,18–20} The risk does not seem to be different when comparing CD patients with UC patients.^{20,21} Our Portuguese cohort does not seem to differ from some of the cohorts described in the literature.²² In our study, similarly to the Brazilian cohort of 1093 IBD patients, the majority of included patients had extensive disease (55% *versus* 56.7% with pancolitis and 44% *versus* 48.5% with ileocolonic CD, comparing our cohort with the Brazilian, respectively) or complicated CD (71%

Table 4. Description of the study population after the follow-up period of 36 months.

Characteristics	Ulcerative colitis (<i>n</i> = 49)	Crohn's disease (<i>n</i> = 100)	<i>p</i> value
Hospitalization, <i>n</i> (%)			
Yes	20 (40.8)	36 (36.0)	0.569 ^{a,1}
IBD-related	8 (16.3)	28 (28.0)	
Not IBD-related	12 (24.5)	8 (8.0)	
No	29 (59.2)	64 (64.0)	
Surgery, <i>n</i> (%)			
Yes	9 (18.4)	24 (24.0)	0.437 ^{a,2}
IBD-related	2 (4.1)	18 (18.0)	
Not IBD-related	7 (14.3)	6 (6.0)	
No	40 (81.6)	76 (76.0)	
Oral corticosteroids, <i>n</i> (%)			
Yes	10 (20.4)	17 (17.0)	0.612 ^a
No	39 (79.6)	83 (83.0)	
Neoplasia, <i>n</i> (%)			
Yes	2 (4.1)	0 (0)	0.107 ^b
No	47 (95.9)	100 (100.0)	
Pregnancy, <i>n</i> (%) †			
Yes	4 (13.8)	1 (1.9)	0.050^b
No	25 (86.2)	52 (98.1)	
IBD, inflammatory bowel disease. ^a Chi-square test; ^b Fisher's test. ¹ <i>p</i> value relative to the comparison of the groups 'with hospitalization' and 'without hospitalization'. ² <i>p</i> value relative to the comparison between 'with surgery' and 'without surgery'. †Considering only females (<i>n</i> = 82) with ulcerative colitis (<i>n</i> = 29) or Crohn's disease (<i>n</i> = 53).			

versus 69.8% with stricturing or penetrating CD and 30% *versus* 14.9% with perianal involvement, comparing our cohort with the Brazilian, respectively). Whereas the Brazilian cohort reported a 5.1% prevalence of TE during a 5-year follow-up, we did not record any TE during our 3-year follow-up.

Even though most TE occur during active disease,^{14,18} the overall risk of these events is significant during all phases of the disease, supporting the hypothesis of a prothrombotic tendency in IBD regardless of disease activity.^{9,18,20} In our

study, irrespective of IBD phenotype, most included patients were in clinical remission at baseline (57.1% with UC and 65% with CD). Only a small percentage of these patients had severe disease (Harvey–Bradshaw score > 16 in 1% of CD patients and partial Mayo score ≥ 7 in 12.2% of UC patients) or required hospitalization or corticotherapy during follow-up due to a disease flare, in which the hypercoagulable state can be intensified. IBD patients in our center are closely followed in IBD consultations, especially those on biological therapy, who are also monitored in a day hospital during drug infusion. To

avoid severe disease flare, blood samples to assess inflammatory biomarkers and clinical scores to assess disease activity are used on a regular basis. Also, all patients initiated on anti-TNF therapy are submitted to proactive therapeutic drug monitoring during maintenance to ensure optimal drug through levels and improve IBD therapy outcomes. The majority (55.7%) of included patients were under anti-TNF, anti-integrin $\alpha_4\beta_7$ or anti-interleukin 12–23, and a smaller percentage (37.6%) were medicated with nonbiologic immunomodulators or aminosalicylates. Therefore, we can infer that a strict control of disease activity may have contributed to the absence of IBD complications like TE.

In this study, the low percentage of patients with moderate to severe active disease could partially explain the absence of TE.

The effect of other risk factors for thrombosis, such as hospitalization, surgery, pregnancy, and medication, are also important to consider in IBD patients.¹⁸

Corticosteroids are useful in IBD exacerbations, but they are also likely to increase the risk of thrombosis.^{23–25} In fact, these drugs can enhance platelet functions and promote hemostasis, thus it is still controversial whether the thrombotic risk is induced solely by IBD itself.²⁶ However, biological therapy with anti-TNF α seems to decrease the occurrence of these events,^{25,27} while the evidence for vedolizumab and ustekinumab is still limited.¹⁶ In our study, during the 36 months of follow-up, almost 20% of UC and CD patients needed oral corticosteroids due to active disease, but most patients (55.7%) were also on biological therapy as a maintenance therapy. This could have attenuated the adverse effects of corticosteroids regarding its association with venous TE. None of the patients with UC who were medicated with tofacitinib, which is described to be associated with increased odds of TE.²⁸

Patients who are hospitalized due to IBD complications usually present with a severe flare and need intravenous corticosteroids, therefore increasing the risk of TE. However, factors like fluid depletion or prolonged immobilization can affect the haemostatic system during hospitalization, contributing to the finding that hospitalization and surgery are associated with a higher probability of TE regardless of disease activity or

the reason of admission.^{18,24,29} According to ECCO guidelines, subcutaneous prophylactic heparin or low molecular weight heparin is indicated to reduce the likeliness of venous TE; prophylactic TE treatment should be withheld only in patients with severe lower intestinal bleeding.³⁰ However, some studies report that thromboprophylaxis rates among hospitalized patients, particularly in medical services, are low.^{15,16}

Although there was no statistically significant difference in hospitalization rates during the 36 months of follow-up, a higher number of CD patients required hospitalization or surgery compared with patients with UC (28.0 *versus* 16.3% and 18.0 *versus* 4.1%, respectively), but none had experienced TE. Also, like previously stated, all patients hospitalized or submitted to surgery were given enoxaparin in a prophylactic dose, which also could have contributed to the absence of TE during follow-up.

Pregnancy is a known hypercoagulable state, and the occurrence of TE in pregnant women is reported to be 4 to 6 times more frequent than in nonpregnant women.^{16,18,31} As described earlier, IBD doubles the likelihood of TE in pregnant women when compared with non-IBD patients,³² mainly in the third trimester and also in the first three weeks postpartum.^{31,33} As stated for nonpregnant IBD patients, disease activity seems to be related to increased odds for TE during pregnancy,^{5,9,18,31} with a reported 8-fold higher risk of vascular events in pregnant women with IBD flares.³² In our study, only a few women became pregnant during the follow-up; adequate disease control was achieved, in all cases, before conception, which could explain the lack of vascular complications in these patients.

Coagulation cascade and fibrinolytic system in IBD

Inflammatory states and the coagulation system are related mainly due to biological and biochemical effects of the inflammatory pathways in the hemostatic system.^{14,20,27}

Many haemostatic alterations that led to a hypercoagulable state appear to be related to disease activity in IBD.^{1,6,8} At the molecular level, the upregulation of the inflammatory pathways with the release of cytokines (interleukin-6 and tumor necrosis factor, *p.e.*), activates the coagulation

system and creates a prothrombotic state that causes abnormalities in the coagulation cascade (higher levels of coagulation factors V, VII, VIII, X, XI, XII, fibrinogen and prothrombin) and on natural coagulation inhibitors (lower levels of antithrombin, protein C and protein S, thrombomodulin, tissue factor-pathway inhibitor and endothelial protein C receptor). This state is also associated with an impairment of the fibrinolytic system (higher levels plasminogen activator inhibitor 1, thrombin-activatable fibrinolysis inhibitor and of D-dimer, and lower levels of tissue plasminogen activator), immune system (higher levels of anti-beta-2-glycoprotein-I and anti-cardiolipin antibodies) endothelium, and platelets (higher number and reactivity).^{5,8,14–16,18,20} In IBD patients, the role of inherited thrombophilias (like factor V Leiden, prothrombin G20210A mutation, deficiencies in protein C, protein S and antithrombin, PAI-1 mutation, factor XIII mutation, and the MTHFR C677 T mutation) in TE is similar to that observed in the general population.^{14,16}

Whether the reported modifications are a consequence of inflammation or are inherent to IBD regardless of clinical activity is still under debate.^{20,34,35} Also, if they differ with IBD subtypes and how they correlate with TE occurrence is still unclear.¹⁸ Research on acquired and inherited causes of thrombophilia has shown that although these mutations confer a higher risk of TE^{18,36} their prevalence does not appear to be increased in the IBD population.^{14,27,37} However, these aspects were not evaluated in our study.

Published data regarding coagulation factor variations in IBD patients and their effect on increasing thrombotic risk is limited and incongruous.³⁸ Clotting times (apTTT and PT) in IBD patients seem to be comparable with those of healthy patients.^{39,40} However, other studies have found that IBD patients have prolonged PT.^{2,34} Regarding coagulation factors, while some studies report higher levels of factors VII, IX, and X in IBD patients,^{2,34,40} others state their similarity to healthy controls.³⁹ Likewise, coagulation and fibrinolysis regulators, as well as plasminogen levels, also showed variable differences between IBD and healthy patients.^{34,38,41} With respect to D-dimer levels, studies are more consistent, reporting higher values in IBD, mostly in active disease.^{14,39,42}

Concerning CD and UC differences, some series reported higher activity of factor VII in CD

patients,³⁴ while UC patients showed higher values of factor X.² In other series, UC patients seemed to have higher PT and higher factor V and VIII levels, but DC patients presented with increased levels of plasminogen.²

So far, the only consistent changes in IBD patients' hemostatic systems, either for CD or UC, include higher levels of factor V, VIII, fibrinogen, plasminogen activator inhibitor-1, Von Willebrand factor, and D-dimer.^{2,12,38–40} However, the link between the referred changes and the occurrence of TE has not been thoroughly evaluated to date.

Although our study did not compare IBD and healthy patients, the addressed components of the coagulation cascade and fibrinolytic system did not seem to vary in great magnitude from their reference values, which can partially explain the absence of reported TE during follow-up. However, active IBD (defined by Harvey–Bradshaw score and Partial Mayo score > 4) was associated with higher values of D-dimer both in UC and CD, and higher levels of fibrinogen and factor VIII in CD ($p=0.043$) and UC ($p=0.019$) patients, respectively, with moderate to severe disease. Also, when comparing CD with UC patients, our study reveals higher levels of plasminogen in CD patients ($p=0,035$). Since no TE occurred during follow-up, we cannot assess the clinical relevance of those coagulation disorders regarding TE occurrence.

The absence of TE in our study can also be somehow related to our limitations. In this study, although the follow-up time was adequate to find TE during the IBD course, the small sample size may have influenced the fact that no TE were recorded. Studies describing higher incidence rates of TE in IBD are conducted with a much larger number of patients and shorter follow-up periods. Also, all of our patients that needed hospitalization or surgery (regardless of admission motif) were given enoxaparin in a prophylactic dose, as recommended by the guidelines,³⁰ which could have contributed to the absence of TE during follow-up.

Despite our limitations, we herein provide the first Portuguese prospective study that thoroughly describes an IBD population followed on a regular basis, with reports and records of all events and complications during follow-up in a dedicated database.

In conclusion, the hypercoagulable state in IBD patients emerges in a multifactorial context, so that acquired and inherited risk factors for TE, as well as changes in coagulation parameters, do not fully account for the prothrombotic predisposition in this population. In this regard, the clinical relevance of measuring coagulation parameters in IBD patients is limited.

Author contribution(s)

Ana Catarina Carvalho: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Juliana Pinho: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Visualization; Writing – review & editing.


Eugénia Cancela: Conceptualization; Funding acquisition; Investigation; Methodology; Visualization; Writing – review & editing.

Hugo Marcelo Vieira: Data curation; Formal analysis; Software; Visualization; Writing – review & editing.

Américo Silva: Conceptualization; Funding acquisition; Visualization; Writing – review & editing.

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A.C.C., J.P., E.C., H.M.V., A.S. declare that there is no conflict of interest. P.M. received consulting fees and support to travel to meetings from the following companies: Abbvie, Falk Pharma, Ferring, Pfizer, Takeda, and Janssen.

Supplemental material

Supplemental material for this article is available online.

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