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Rotational Thromboelastometry Coagulation Parameters (ROTEM®) May be Discriminative for Active Inflammatory Bowel Disease: A Prospective Observational Study

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ABSTRACT

Background & Aims: Inflammatory bowel disease (IBD) is associated with increased risk of thromboembolic events. The rotational thromboelastometry (ROTEM®) is a validated integrative assessment of coagulation, but it has never been studied in IBD patients.
Methods: We performed a monocentric prospective observational study in a national tertiary center. Adult IBD patients underwent ROTEM® analysis on admission to our IBD Department. Parameters evaluated with ROTEM® tests (INTEM, EXTEM and FIBTEM) were clotting time (CT), the time of clot formation (CFT), clot firmness amplitude after 5 and 10 minutes (A5 and A10) and maximum clot firmness (MCF). ROC curves were performed in order to evaluate the ability of ROTEM® to predict active IBD.
Results: Several ROTEM® parameters were significantly associated with active IBD compared to patients in remission, towards a hypercoagulable status for patients with active disease: CT, CFT, A5, A10, MCF. ROC analysis demonstrated that parameters related to clot robustness showed a very good prediction ability of active IBD (AUC >0.8): A5, A10, MCF in INTEM ($p<0.001$), in EXTEM ($p<0.001$) and MCF in FIBTEM ($p<0.001$). ROTEM® parameters showed high correlations with inflammation markers as C-reactive protein (CRP) and faecal calprotectin (FC).
Conclusions: Our study showed that ROTEM® parameters are modified in patients with active IBD, being correlating with inflammation markers and demonstrating a high prediction ability of active IBD. Future research is needed to validate ROTEM® as a method to discriminate patterns of active IBD and to guide anticoagulant therapy in patients with active IBD.

Key words: ROTEM® – thromboelastometry – inflammatory bowel disease – coagulation – Crohn's disease – ulcerative colitis.

Abbreviations: A10-E: A10 in EXTEM; A10-I: A10 in INTEM; A5-E: A5 in EXTEM; A5-I: A5 in INTEM; APTT: activated partial thromboplastin time; AUC: area under curve; CD: Crohn's disease; CDAI: CD activity index; CFT: clotting formation time; CFT-E: clotting formation time in EXTEM; CFT-I: clotting formation time in INTEM; CI: confidence interval; CRP: C-reactive protein; CT: clotting time; CT-E: clotting time in EXTEM; CT-F: clotting time in FIBTEM; CT-I: clotting time in INTEM; EIM: extraintestinal manifestation; FC: fecal calprotectin; FG: fibrinogen IBD: inflammatory bowel disease; INR: international normalized ratio; IQR: interquartile range; JAKi: Janus Kinase inhibitor; MA: maximum amplitude; MCF: maximum clot firmness; MCF-E: maximum clot firmness in EXTEM; MCF-F: maximum clot firmness in FIBTEM; MCF-I: maximum clot firmness in I; OR: odds ratio; PLT: platelet count; PT: prothrombin time; ROC: receiver operating characteristic; ROTEM®: rotational thromboelastometry; TEG®: thromboelastography; TNF: tumor necrosis factor; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing condition of unknown etiology that triggers an uncontrolled inflammatory response targeting the gastrointestinal tract often associating systemic involvement with a wide range of extraintestinal manifestations (EIMs), including thrombosis. Patients with IBD have a 3.6-fold risk of thromboembolic events compared with non-IBD controls that increases with active disease requiring prophylactic anticoagulation during flares [1, 2]. The underlying mechanisms of thrombosis in IBD are not well

understood, but abnormalities in coagulation factors such as high levels of fibrinogen, thrombocytes, factors V, VIII and plasminogen in patients with IBD have been described [3-5]. Even though the increased risk of both venous and arterial thromboembolic events in active ulcerative colitis (UC) and Crohn's disease (CD) might suggest a relation with inflammation, the prothrombotic status has not been demonstrated in other systemic inflammatory conditions such as rheumatoid arthritis or coeliac disease [2, 6].

Inflammatory bowel disease is diagnosed with less frequency than in the general population in patients with coagulopathy disorders such as haemophilia A, B, Von Willebrand disease, raising the interesting hypothesis that abnormalities in coagulation process may have a role in IBD pathogenesis and evolution [7, 8]. Conventional coagulation tests provide limited information on the qualitative coagulation process. They only provide quantitative measurement of coagulation variables (platelets and fibrinogen). Rotational thromboelastometry (ROTEM®) is a point of care test with rapidly available results which evaluates the hemostatic process as a whole: clot formation, strength and lysis [9, 10]. ROTEM® can give more detailed information on the changes in hemostasis parameters in IBD depending on disease evolution. Exploration with ROTEM® could provide further insight into the causal pathophysiological relationship between inflammation associated with IBD and thrombotic risk. Such information may help in selecting the patients in need for thromboprophylaxis. To date, no study has evaluated the coagulation profile with ROTEM® in IBD during inactive and active phases.

The main objective was to describe the modification of ROTEM® coagulation profiles in patients with IBD, according to the disease activity status. The secondary aims were: (i) to explore the relation between ROTEM® parameters, inflammatory markers, standard coagulation tests for patients with active disease or clinical remission (ii) to evaluate the ability of ROTEM® parameters to predict the presence of an active IBD status.

METHODS

Ethics and Study Design

The study was conducted with the approval of the Fundeni Clinical Institute Ethics Committee (21192/16.04.2021) and was conducted according to the Declaration of Helsinki, Good Clinical Practice recommendations. All included patients received written information and gave written consent to participate to the study.

We performed a monocentric prospective observational study in a national university tertiary center (Bucharest, Romania). We included consecutive adult patients with IBD regardless of disease activity who presented to our IBD Department from May 2021 to August 2021. Further we extended the inclusion period from February to April 2022 when we included consecutive patients with active IBD only. The exclusion criteria were time since disease diagnosis less than one-year, other associated diagnoses except IBD, complications of IBD such as active infections or current EIMs, concomitant medication for other conditions including anticoagulants and antiplatelet therapy, history of surgery or other invasive procedures in the last 6 months and pregnancy.

Disease activity was evaluated using clinical scores: Crohn's Disease Activity Index (CDAI) for CD and Mayo clinical score for UC [11]. Active disease was defining by a CDAI score equal or higher than 150 for CD and a score equal or higher than 3 for UC [11]. The diagnosis of IBD was made according to standard recommendations [9]. The phenotype of both UC and CD were assessed using the Montreal classification [12]. None of the patients had current or previous history of thromboembolic events.

Patients' clinical characteristics and prescribed treatment data were collected. Markers of inflammation such as C-reactive protein (CRP) and fecal calprotectin (FC) were also assessed and noted.

Coagulation Tests

For ROTEM® evaluation, 2.7 ml of citrated blood were collected from each patient. Blood samples were analysed using a ROTEM® (ROTEM Delta; Instrumentation Laboratory, Bedford, Massachusetts, USA) according to the manufacturer's protocol. Three tests were used for ROTEM® analysis: INTEM and EXTEM that use activators targeting intrinsic and extrinsic coagulation pathway respectively and FIBTEM that evaluates the role of fibrinogen on the clot firmness after the inhibition of the platelet function. Parameters that were evaluated for INTEM and EXTEM were represented by: clotting time (CT) expressed in seconds, the time of clot formation (CFT) expressed in seconds, clot firmness amplitude after 5 and 10 minutes (A5 and A10), expressed in millimetres and maximum clot firmness (MCF), expressed in millimetres. For FIBTEM we analysed only MCF and CT.

Conventional coagulation parameters were determined as part of a routine evaluation which included fibrinogen, platelet count, international normalized ration (INR), prothrombin time (PT), activated partial thromboplastin time (APTT).

Statistical Analyses

Data were anonymously prospectively collected in a database, and they were analysed using RStudio (Version 1.1.447 – © 2009-2018 RStudio, Inc., Wien, Austria). Normal distribution for continuous variables was evaluated by histograms and by the Shapiro-Wilk test. The results were presented as median with [25%-75%] interquartile range (IQR).

The coefficient of variation in the study cohort was calculated for each coagulation parameter. Student's test or Mann-Whitney test were used as appropriate for comparisons of continuous variables. Chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. The relation between the markers of inflammation (CRP and FC) and tests of coagulation was evaluated using Spearman's correlation tests, as appropriate.

Receiver operator characteristic (ROC) analyses based on the ability to predict the active IBD status were performed for ROTEM® parameters, inflammatory markers and standard coagulation tests.

The interactions between standard coagulation tests, ROTEM® parameters, and with or without the inflammation markers were further explored using a principal component

analysis, followed by a factorial analysis. The R package "psy" was used [13]. As the database has no missing data, we did not use the imputation strategy.

A p value< 0.05 was considered statistically significant.

RESULTS

Patients' Characteristics

Seventy-four patients were included, comprising 46 patients with CD and 28 patients with UC. The patients' characteristics are summarized in Table I, comparatively for active and inactive disease. From the patients in the CD group, 24 (54.5%) had ileocolonic localization of the disease, 20 (45.4%) colonic and 2 (3.7%) ileal. In the UC group, 14 (50%) of patients had pancolitis, 8 (28.5%) left side colitis and 6 (21.4%) proctitis.

According to clinical activity scores 54 (72.9%) of IBD patients were in clinical remission and 20 (27%) had active disease. The analysis of inflammatory markers showed a CRP median value of 2.8 mg/L [0.9-4.9] for patients in clinically remission, and respectively 17.1 mg/L [2.7-55] for patients with active disease (p<0.001). The FC median value was 138 microg/g [46-508] for inactive disease, and 617 microg/g [291-1000] for active disease, respectively (p<0.001). The maximum value for FC was selected as 1000 microg/g and the lowest value as 5 microg/g representing the laboratory limits for quantitative quantification.

Table I. Patients' characteristics

Characteristics	Inactive (n=54)	Active (n=20)	p
Age(years), median [IQR]	36 [29-45]	35 [26-44]	0.551
Sex (male), n(%)	28 (52)	10(50)	0.887
BMI(kg/m^2), mean±SD	21.3±1.3	20.5±1.2	0.018
Active smoking, n (%)	7 (13)	7 (35)	0.032
Crohn's disease, n (%)	34 (63)	12 (60)	0.815
CD phenotype, n(%)			
Ileal	2 (3.7)	0 (0)	1
Colonic	13 (24)	7 (35)	0.347
Ileocolonic	19 (35)	5 (25)	0.406
Perianal	8 (15)	5 (25)	0.307
Inflammatory	10 (19)	8 (40)	0.056
Stricturing	11 (20)	0 (0)	0.030
Penetrating	14 (26)	5 (25)	0.935
UC phenotype, n(%)			
Proctitis	4 (7)	2 (10)	0.659
Left-side colitis	6 (11)	2 (10)	1
Pancolitis	10 (19)	4 (20)	1
Disease behaviour, n (%)			
[1]Mayo score,median [IQR]	0 [0-0.75]	5 [4-7]	<0.001
[2]CDAI score,median [IQR]	0 [0-14]	189 [160-278]	<0.001
Treatment			
CS (yes), n(%)	1 (2)	4 (20)	0.017
5-ASA (yes), n(%)	5 (9)	2 (10)	1
Azathioprine (yes), n (%)	9 (17)	4 (20)	0.739
Adalimumab (yes),n (%)	10 (19)	0 (0)	0.053
Infliximab (yes),n (%)	21 (39)	3 (15)	0.057
Vedolizumab (yes), n (%)	13 (24)	3 (15)	0.532
Ustekinumab (yes), n (%)	6 (11)	3 (15)	0.696
Tofacitinib (yes), n (%)	1 (2)	1 (5)	0.470

BMI: body mass index; CD: Crohn's disease; UC: ulcerative colitis;, CDAI: Crohn's disease activity index; CS: corticosteroids; 5-ASA:5-aminosalicylic acid. [1] For patients with UC; [2]For patients with CD.

ROTEM® Analysis Results

The ROTEM® results are presented in Table II, comparatively for active and inactive disease. The overall ROTEM® parameters did not show major changes comparing with the normal values.

Table II. Laboratory results

Coagulation tests	Inactive (n=54)	Active (n=20)	p-value
ROTEM: EXTEM			
CT (s),	59 [53-63]	68 [60-73]	0.001
CFT (s)	105 [90-121]	69 [57-87]	<0.001
A5 (mm)	45 [41-49]	59 [50-64]	<0.001
A10 (mm)	56 [52-60]	69 [60-72]	<0.001
MCF (mm)	65 [59-66]	73 [66-76]	<0.001
ROTEM: INTEM			
CT (s)	171 [161-184]	164 [159-183]	0.292
CFT (s)	69 [57-88]	50 [42-57]	<0.001
A5 (mm)	50 [45-54]	60 [53-67]	<0.001
A10 (mm)	59 [54-62]	68 [63-74]	<0.001
MCF (mm)	65 [62-67]	74 [69-77]	<0.001
ROTEM: FIBTEM			
CT (s)	57 [50-62]	62 [57-70]	0.030
MCF (mm)	14 [11-18]	26 [18-33]	<0.001
Standard coagulation data			
PLTx109 /L	290 [236-339]	414 [332-516]	<0.001
PT (s)	12.9 [12.4-13.3]	13.7 [13.1-14.7]	0.001
APTT (s)	28 [27-30]	27 [25-29]	0.043
INR	0.97 [0.93-1]	1.01 [0.96-1.17]	0.004
Fibrinogen (mg/dL)	340 [300-400]	470 [390-640]	<0.001
Inflammatory markers			
CRP (mg/L)	2.8 [0.9-4.9]	17.1 [2.7-55]	<0.001
FC (microg/g)	138 [46-508]	617 [291-1000]	<0.001

CT: clotting time; CFT clot formation time; MCF: maximum clot firmness; PLT: platelet; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CRP: C-reactive protein.

Several ROTEM® parameters were statistically significantly different in patients with active disease compared with patients in remission. EXTEM results found a statistically significant difference of CT (s): 68 (60-73) vs 59 (53-63) (p=0.001); CFT (s): 69 (57-87) vs 105 (90-121) (p<0.001); A5 (mm): 59 (50-64) vs 45 (41-49) (p<0.001); A10 (mm): 69 (60-72) vs 56 (52-60) (p<0.001; and MCF (mm): 73 (66-76) vs 65 (59-66) (p<0.001), between patients with active disease and patients in clinical remission. INTEM analysis found statistically significant difference in CFT (s): 50 (42-57) vs 69 (57-88) (p<0.001); A5 (mm): 60 (53-67) vs 50 (45-54) (p<0.001); A10 (mm): 68 (63-74) vs 59 (54-62) (p<0.001); MCF (mm): 74 (69-77) vs

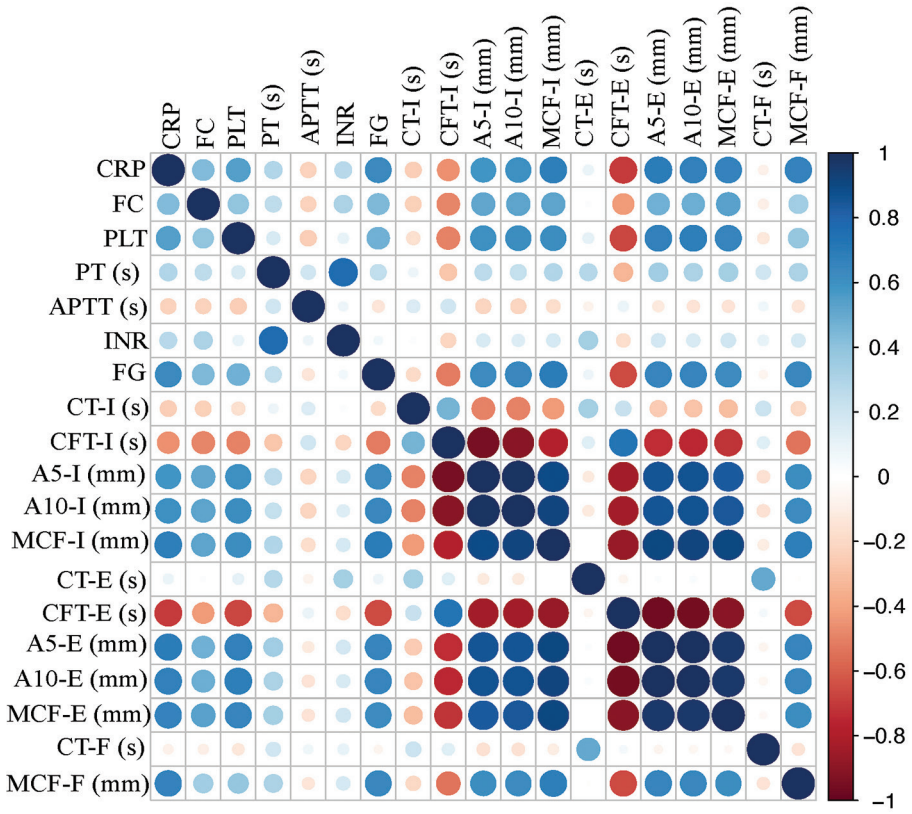

Fig. 1. Correlation matrix between ROTEM® parameters, standard coagulation tests and inflammatory markers.

65 (62-67) (p<0.001), between active disease and patients in clinical remission. FIBTEM test showed a significantly higher CT (s): 62 (57-70) and MCF (mm): 26 (18-33) for patients with active disease than for those in clinical remission [57 (50-62), p=0.03; respectively 14 (11-18), p<0.001].

Prediction of Active IBD

The ROC analysis results are presented in Table III. Several ROTEM® parameters showed a very good prediction ability of active IBD, with AUC > 0.8: A5 (INTEM) (AUC of 0.83, 995%CI: 0.71-0.95, p<0.001); A10 (INTEM) (AUC of 0.83, 95%CI: 0.71-0.95, p<0.001); MCF (INTEM) (AUC of 0.88, 95% CI: 0.79-0.98, p<0.001); A5 (EXTEM) (AUC of 0.86, 95% CI: 0.76-0.96, p<0.001); A10 (EXTEM) (AUC of 0.87, 95% CI: 0.78-0.96, p<0.001; MCF (EXTEM) (AUC of 0.86, 95% CI: 0.76-0.96, p<0.001); and MCF (FIBTEM) (AUC of 0.81, 95% CI: 0.70-0.92, p<0.001).

Other standard coagulation tests and inflammatory markers also showed a high predictivity of active IBD: fibrinogen concentration (AUC of 0.85, 95%CI: 0.76-0.95, p<0.001), platelets count (AUC of 0.85, 95%CI: 0.72-0.92, p<0.001), CRP (AUC of 0.82, 95%CI: 0.70-0.94, p<0.001), and FC (AUC of 0.81, 95%CI: 0.75-0.94, p<0.001).

Inflammation and ROTEM® Tests Results

The correlations between markers of inflammation (CRP and FC) and ROTEM® parameters are shown in Table IV and Fig. 1. Several ROTEM® parameters were found to be correlated (correlation coefficient rho > 0.5 or <-0.5, p<0.001) with CRP: A5 (INTEM) (rho= 0.588, p<0.001), A10 (INTEM) (rho= 0.608, p<0.001), MCF (INTEM) (rho=0.681, p<0.001), CFT (EXTEM) (rho=0.691, p<0.001), A5 (EXTEM) (rho=0.691,p<0.001), A10 (EXTEM) (rho=0.675,p<0.001), MCF (EXTEM) (rho=0.664,p<0.001), and MCF (FIBTEM) (rho=0.664, p<0.001).

Regarding the correlation between ROTEM® parameters and FC, high statistically significant correlations were found for A5 (INTEM) (rho=0.51, p<0.001), A10 (INTEM) (rho=0.522, p<0.001), MCF (INTEM) (rho=0.522, p<0.001), and MCF (EXTEM) (rho=0.535, p<0.001).

Principal Component Analysis and Factorial Analysis Results and Interpretation

The relationship between ROTEM® parameters and standard coagulation was evaluated by using principal component analysis combined with factorial analysis (Fig. 2D and Supplementary file, Fig. 1 (spherical representation). The visual interpretation of these figures suggests that ROTEM® parameters and standard coagulation tests are not fully superposable. As expected, the A5, A10, MCF are positively correlated with the platelets count and fibrinogen concentration. Furthermore, INR, PT and CT (EXTEM) and CT (FIBTEM) are correlated.

Based on the factorial analysis (Table V), the coagulation data is explained by 2 dimensions (p<0.001, the screen plot with Eigen values is presented in Supplementary file, Fig. 2). The most important contributors to factor 1 were parameters related to clot robustness (A5, A10, MCF, platelets and fibrinogen). The most important contributors to factor 2 were parameters related to coagulation initiation (CT, PT and INR).

Table III. Receiver-operator characteristic (ROC) analyses for the prediction of active IBD

Variables	AUC	95% CI	p
ROTEM: EXTEM			
CT (s),	0.75	0.62-0.88	0.001
CFT (s)	0.14	0.05-0.22	-
A5 (mm)	0.86	0.76-0.96	<0.001
A10 (mm)	0.87	0.78-0.96	<0.001
MCF (mm)	0.86	0.79-0.98	<0.001
ROTEM: INTEM			
CT (s)	0.42	0.27-0.57	-
CFT (s)	0.17	0.05-0.29	-
A5 (mm)	0.83	0.71-0.95	<0.001
A10 (mm)	0.83	0.71-0.95	<0.001
MCF (mm)	0.88	0.79-0.98	<0.001
ROTEM: FIBTEM			
CT (s)	0.67	0.53-0.80	0.030
MCF (mm)	0.86	0.76-0.96	<0.001
Standard coagulation data			
PLTx109 /L	0.85	0.72-0.92	<0.001
PT (s)	0.75	0.61-0.89	0.001
APTT (s)	0.35	0.21-0.49	-
INR	0.72	0.58-0.85	0.004
Fibrinogen (mg/dL)	0.85	0.76-0.95	<0.001
Inflammatory markers			
CRP (mg/L)	0.82	0.70-0.94	<0.001
Fecal calprotectin (microg/g)	0.81	0.75-0.94	<0.001

AUC: area-under-curve; CI: confidence interval; IBD: inflammatory bowel disease; For the rest of abbreviations see Table II.

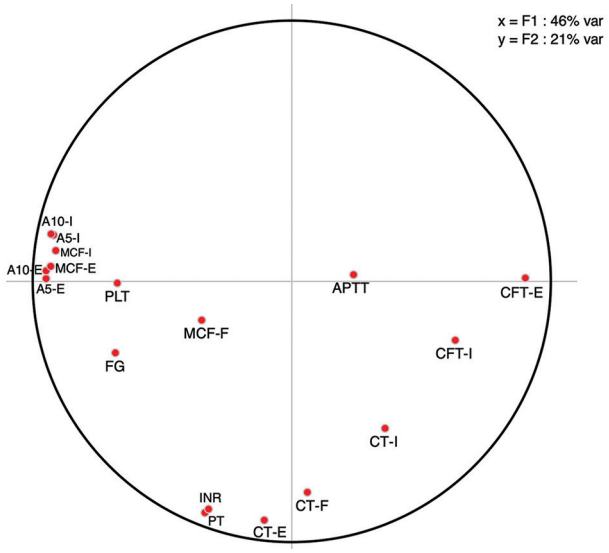

Fig. 2. Principal component analysis. Bidimensional representation of the relation between ROTEM® parameters and standard coagulation tests.

DISCUSSION

Our study is the first one to report values of ROTEM® variables in patients with IBD considering the state of the disease (active/remission). Our results can be summarized as follows: (i) Active IBD patients have ROTEM® parameters slightly in favor of a hypercoagulable status compared to patients in clinical remission, (ii) the modified ROTEM® parameters showed a strong correlation with the markers of inflammation, particularly the parameters associated with clot firmness, and (iii) the ROTEM® parameters were clinically relevant predictors of active IBD.

Our findings are in concordance with the European guidelines, which recommend thromboprophylaxis for all IBD hospitalized patients, after recent surgery and in outpatients with active disease [14]. Although thromboembolic events are associated with disease activity, a high rate of thrombosis is also reported during disease remission [14,15]. We did not find any alterations in coagulation parameters of patients in clinical remission, but we could not explore the transition from active to remission phases. Such an exploration could allow clinicians to decide on the duration of thromboprophylaxis following disease activation.

As we performed the first ROTEM® evaluation of patients with IBD, comparator studies are lacking. There are only three smaller reported cohorts in the literature that evaluated the role of a similar method (Tromboelastography, TEG®) in evaluating the hypercoagulable state in IBD. Both TEG® and ROTEM® use similar principles in assessment of blood clotting with whole blood, but the results of the two devices are not interchangeable

Table IV. Correlations between CRP, FC and coagulation tests

Coagulation tests	CRP		FC	
	Rho Coefficient	p	Rho Coefficient	p
ROTEM: INTEM				
CT (s)	-0.245	0.036	-0.234	0.045
CFT (s)	-0.455	<0.001	-0.486	<0.001
A5 (mm)	0.588	<0.001	0.516	<0.001
A10 (mm)	0.608	<0.001	0.527	<0.001
MCF (mm)	0.681	<0.001	0.522	<0.001
ROTEM: EXTEM				
CT (s)	0.096	0.415	0.023	0.843
CFT (s)	-0.691	<0.001	-0.429	<0.001
A5 (mm)	0.691	<0.001	0.476	<0.001
A10 (mm)	0.675	<0.001	0.482	<0.001
MCF (mm)	0.664	<0.001	0.535	<0.001
ROTEM: FIBTEM				
CT (s)	-0.088	0.456	-0.096	0.417
MCF (mm)	0.663	<0.001	0.348	0.002
Standard coagulation				
Platelets (x109/l)	0.548	<0.001	0.393	0.001
PT (s)	0.291	0.012	0.253	0.03
APTT (s)	-0.229	0.05	-0.221	0.058
INR	0.271	0.02	0.311	0.007
Fibrinogen (mg/dl)	0.636	<0.001	0.445	<0.001

FC: fecal calprotectin; For the rest of abbreviations see Table II.

Table V. Factorial analysis of coagulation tests results

Variables	Factor 1	Factor 2
EXTEM		
CT		0.855
CFT	-0.953	
A5	0.993	
A10	0.998	
MCF	0.972	
INTEM		
CT	-0.244	0.353
CFT	-0.477	
A5	0.807	
A10	0.818	
MCF	0.831	
FIBTEM		
CT	-0.147	0.730
MCF	0.288	0.186
Standard coagulation		
Platelets	0.654	
PT	0.249	0.951
APTT	-0.193	
INR	0.215	0.942
Fibrinogen	0.642	0.297

For abbreviations see Table II.

because they use different activators [9, 16]. Shen et al. [17] included 63 IBD patients (34 with CD and 29 with UC) with 21 (61.8%) and 19 (65.5%) patients with active CD respectively UC. The results were interpreted comparatively with the TEG® parameters obtained from 53 controls. Their results showed a hypercoagulable state of all IBD patients when compared to controls defined by differences in TEG® parameters R, k, α Angle and MA, that increases among IBD patients with the degree of clinical activity of the disease [17]. Knyazev et al. [18] included 15 patients with UC and compared TEG® parameters with extended coagulation tests according to clinical activity of the disease. They showed a hypercoagulable state of all patients with UC regardless of disease activity and a higher sensitivity of TEG® when compared to standard coagulation tests [18]. Holubar et al. [19] included 19 patients with IBD and performed TEG® evaluation prior to surgery, revealing that 14/19 (74%) of patients had a hypercoagulable TEG® profile [19]. All three mentioned studies showed modifications of the TEG® parameters in the direction of a procoagulant status in IBD patients with clinically inactive disease.

Contrary to these TEG® studies we found a normal ROTEM® coagulation profile for the patients in clinical remission. This difference might be explained by several factors. Firstly, Shen Y et al. [17] included a significantly smaller number of patients with inactive IBD compared to our study, and all three studies gave no information about the IBD treatment. Regarding the two other smaller studies we cannot make any assessments concerning the characteristics of patients in clinical remission because of unavailable data. However, the prescribed treatment can play a role in influencing the coagulation status and should be discussed. Corticosteroids are known to increase the risk of thrombosis, and the recently approved Janus Kinase inhibitors (JAKi) have reported thrombotic events as adverse events, limiting their use in higher doses, particularly for patients with other risk factors for thrombosis [20, 21]. Of the patients included in our study, 49/74 (66.2%) had been under maintenance treatment with biologics and JAKi. 35/74 (47.2%) patients were receiving anti-tumour necrosis factor (TNF)-α inhibitors. The antithrombotic role of TNF-α antagonists has been demonstrated in previous studies being related to both its anti-inflammatory action and specific anticoagulant mechanisms [21, 22]. 32/35 (91%) of patients in treatment with (TNF-α) inhibitors were in clinical remission and had normal standard coagulation values and no modification in ROTEM® parameters. Secondly, the different results might be due the lack of interchangeability of ROTEM® and TEG® results.

Clinical Relevance of Our Findings and Perspectives

Even though we presented only exploratory data, our findings raise the questions whether disease remission is responsible for the normal coagulation profile in IBD patients and to what extent the IBD treatment for therapeutic controlled remission is able to reverse the hypercoagulant status of the disease. Further studies are required with more heterogenous IBD cohort profiles and especially the time-dependent changes of ROTEM parameter during the transition from active disease to remission.

The relationship between IBD and coagulopathy is not fully understood. Although there are reports about perturbation in coagulation factors behavior in IBD and genetic abnormalities there is insufficient data to state that the findings are responsible for thromboembolic events in these patients [15, 23]. Identifying coagulation patterns of the disease is of interest in clinical practice, as several ROTEM® parameters are strongly correlated with inflammation markers and can discriminate active disease from clinical remission state. This possible discriminative potential should be investigated in further studies.

Providing a more comprehensive evaluation of the coagulation process, ROTEM® may help to establish the duration of anticoagulant therapy in patients with active IBD. Also, a potential role of ROTEM® may be in selecting patients in need of anticoagulation among the subgroup with inactive IBD but with concomitant corticosteroids or JAKi treatments.

Limits

Our study can be criticized on several aspects. First, the open, monocentric, observational design does not allow for any causality inference.

Secondly, we included a relatively small number of patients. However, this limit should be considered in the context of a first, exploratory study. This reported cohort was larger than those of other related studies. The limits of the used statistical analyses should also be discussed from the point of view of an exploratory design. We presented univariate comparisons, bivariate correlations, and the multivariable logistic regression was restricted by the low number of patients. Nevertheless, the multifaceted statistical approach might, at least partially, counterbalance this limitation.

Thirdly, we only evaluated clinical activity of the disease. In our study the median values of FC were increased in both active and inactive disease with median values of 617 (291-1000) and 138 (291-1000) respectively. Although at the moment there is no agreement upon the appropriate cut-off value of FC to predict mucosal activity, cut-off values between 100- 250 microg/g are predictable of mucosal active disease [12, 24]. Knowing the good predictive value of FC for mucosal damage, the findings may suggest the existence of mucosal active disease in the studied subgroup of patients in clinical remission. Taking into consideration that the parameters in both standard coagulation and ROTEM® were not modified in patients with clinically inactive disease it would be interesting to evaluate if only systemic and not mucosal inflammation influences coagulation parameters and the risk of thrombosis in these patients.

Fourthly, we did not evaluate clinical outcomes, such as thromboembolic events.

CONCLUSIONS

We present the results of the first study in the literature that evaluates ROTEM® as a method to assess coagulation status in patients with IBD. Our findings showed that ROTEM® parameters are modified in patients with active IBD towards a hypercoagulable state, with no abnormalities seen in ROTEM® parameters in IBD patients under clinical remission with maintenance treatment. Future studies are needed for validate ROTEM®as a method to guide the initiation and duration of anticoagulant therapy in active IBD and in the subgroup of patients with inactive disease but with additional risk factors for thrombosis. Also, the potential of a discriminative role between the active and clinical remission disease should be considered.

Conflicts of interest: None to declare.

Authors' contribution: S.A., G.D., M.D., C.M. conceived and designed the study. C.M., M.D., G.D. recruited the patients and collected the data. S.A. and P.G.G. analysed the data. C.M., S.A., D.L., P.G.G., G.D., M.D. interpreted the results. C.M. and S.A. drafted the manuscript. D.L., P.G.G., M.D. and G.D. critically revised the paper. All the authors approved the final version of the paper.

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