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Fibrinogen, FDP and D-Dimer as Potential Biomarkers for Disease Severity in Ulcerative Colitis: A Retrospective Study

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Purpose: Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease that primarily affects the large intestine. Coagulation abnormalities have been detected in UC patients. This study aimed to evaluate coagulation-related parameters in patients with UC.

Patients and Methods: A total of 364 UC patients were analyzed with 163 female and 201 male. Disease activity was determined according to the Truelove and Witts criteria. The fibrinogen (FIB), D-dimer, fibrin/fibrinogen degradation products (FDP), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were evaluated.

Results: We found higher D-dimer, FDP, FIB levels in severe UC compared with non-severe patients.The area under the curve (AUC) of D-dimer was 0.852 (95% CI 0.805 to 0.898) and the optimum cut-off point was 0.585, with a sensitivity of 80.6% and a specificity of 78.9%. Furthermore, D-dimer and FIB are positively correlated with ESR and CRP levels.

Conclusion: Our results indicate that D-dimer, FDP, and FIB levels are potential biomarkers for disease severity in UC patients.

Keywords: ulcerative colitis, D-dimer, fibrinogen, disease activity

Introduction

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease that primarily affects the large intestine. The incidence of UC is increasing rapidly in China. It is characterized by relapsing and remitting mucosal inflammation.[1,2] Coagulation abnormalities have been detected in UC patients. Inflammatory bowel disease (IBD) is associated with a high risk of venous thromboembolism (VTE).[3–5] Several studies have indicated that IBD is associated with an approximately 2–3 fold elevated risk of VTE compared to healthy controls.[6,7] Venous thromboembolic events in UC patients are associated with significant morbidity and mortality.

D-dimer and fibrin/fibrinogen degradation products (FDP) are involved in many diseases, such as aortic dissection, rheumatoid arthritis, coronavirus disease, severe acute pancreatitis, and cancer. Coagulation parameters play a role in evaluating diseases activity and have prognostic significance.[8–16] Recent evidence indicated that D-dimer levels are related to gut inflammation.[17] The results regarding the relationship between UC activity and coagulation parameters have been inconsistent. Our study aimed to evaluate the coagulation parameters such as fibrinogen (FIB), D-dimer, and FDP among UC patients and its association with disease severity.

Materials and Methods

Study Population

We retrospectively analyzed the electronic medical records of patients with UC admitted to the Jiangsu Province Hospital of Chinese Medicine. This study recruited 364 UC patients between January 2018 and July 2022. UC is diagnosed on the basis of clinical presentation,endoscopic and histopathological findings.[18] We included hospitalized adult patients for

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whom demographic, clinical, and laboratory data could be obtained. Coagulation parameters, including FIB, FDP, and D-dimer levels were collected. The exclusion criteria were as follows: pregnancy, Crohn's disease (CD), indeterminate colitis, age < 18 years, and incomplete laboratory data.

Disease Activity

The Truelove and Witts criteria was used to evaluate disease activity. Patients were classified as mild, moderate, and severe based on the bloody stool frequency, temperature, heart rate, hemoglobin, and erythrocyte sedimentation rate (ESR).[19,20] Disease extent was classified according to the Montreal Classification.

Statistics

Continuous variables are presented as median and interquartile range (IQR). Mann–Whitney and Kruskal–Wallis tests were used to determine the differences between the groups. Categorical variables are expressed as percentages, and the chi-square test was used for comparisons between groups. Spearman's correlation analysis was used to evaluate the association between the variables. Receiver operating characteristic (ROC) curves were plotted to differentiate severe from non-severe UC. P <0.05 was considered statistically significant. Data were statistically analyzed using SPSS 25.0.

Results

Characteristics of Participants

In total, 364 patients with UC were enrolled in this study. The median age was 46 (IQR 34–58) years, ranging from 18 to 78 years. This study included 201 males and 163 females. Of 364 patients, 183 (50.3%) had extensive colitis. 76.9% were taking oral 5-aminosalicylic acid (5-ASA), 14% with steroids, and approximately 6.8% with biologic agents (Table 1). Compared with non-severe UC, white blood cell (WBC) and platelet (PLT) counts increased in severe group. However, hemoglobin levels in patients with severe UC were significantly lower. Severe UC patients have higher levels of ESR and C-reactive protein (CRP) (Table 3).

Table 1 Characteristics of Included Patients

Parameters	n	%
Sex		
Male	201	55%
Female	163	45%
Disease extent		
E1 (Proctitis)	75	20.6%
E2 (Left-sided)	106	29.1%
E3 (Extensive)	183	50.3%
Clinical activity		
Mild	139	38.2%
Moderate	145	39.8%
Severe	80	22%
Treatment		
ASA	280	76.9%
Immunomodulators	2	0.5%
Steroids	51	14%
Biologic agents	25	6.8%

Abbreviation: 5-ASA, 5-aminosalicylates.

Comparison of FIB, FDP, and D-Dimer in Different UC Activity

Truelove and Witts criteria categorized UC activity as mild (n=139), moderate (n=145), and severe (n=80). We observed differences in FDP, FIB and D-dimer among groups. As disease activity increased from mild to severe group, an elevation of FIB, FDP, D-dimer was observed. Comparison of FIB, FDP, and D-dimer in different UC activity were listed in Table 2.

Comparison of FIB, FDP, and D-Dimer Between Severe and Non-Severe UC

The patients were classified into two subgroups according to their severity. There were 284 patients with non-severe UC and 80 severe UC. We found that D-dimer levels in patients with severe UC (1.21; IQR 0.65–2.2) were significantly higher than those in patients with non-severe disease (0.3; IQR 0.23–0.52). The median FDP in patients with non-severe and severe UC were 1.97(IQR 1.44–2.61) and 4.47(IQR 2.48–6.51), respectively (p<0.01). The median FIB was 3.07 (IQR 2.58–3.66) in non-severe UC patients in contrast to 4.41(IQR 3.89–5.32) in severe UC ($p < 0.01$) (Table 3).

Comparison of FIB, FDP and D-Dimer Levels According to Disease Extent

We analyzed the association between disease extent and coagulation parameters. Among the included patients with UC, 75 (20.6%) had proctitis, 106 (29.1%) had left-sided colitis, and 183 (50.3%) had pancolitis. In the acute severe colitis group, the majority of the patients were pancolitis.

Pancolitis showed the higher D-dimer level (0.5; IQR 0.29–1.26), compared to left-sided colitis (0.375; IQR 0.25–0.73) ($p < 0.01$). Pancolitis showed higher FIB levels (3.6; IQR 2.9–4.46) than left-sided colitis (3.27; IQR 2.69–3.9) ($p = 0.011$).

Table 2 Comparison of FIB, FDP, and D-Dimer in Different UC Activity

Parameters	Mild n= 139	Moderate n=145	Severe n=80	P
FIB (g/L)	2.78 (2.46–3.21)	3.39 (2.86–4.13)	4.41 (3.89–5.32)	< 0.01
FDP (μg/mL)	1.67 (1.34–2.12)	2.25 (1.68–3.25)	4.47 (2.48–6.51)	< 0.01
D-dimer(mg/L)	0.26 (0.22–0.35)	0.43 (0.28–0.79)	1.21 (0.65–2.2)	< 0.01

Notes: Reference values: D-dimer (mg/L): 0-0.5; FIB (g/L): 2.0-4.0; FDP (μg/mL): 0-5.0.
Abbreviations: UC, ulcerative colitis; FIB, fibrinogen; FDP, fibrin/fibrinogen degradation products.

Table 3 Comparison of FIB, FDP, D-Dimer and Inflammatory Index Between Patients with Severe UC and Non-Severe UC

Parameters	Severe UC	Non-Severe UC	P
Age	41 (32–55)	48 (35–58)	0.06
FIB	4.41 (3.89–5.32)	3.07 (2.58–3.66)	< 0.01
FDP	4.47 (2.48–6.51)	1.97 (1.44–2.61)	< 0.01
D-dimer	1.21 (0.65–2.2)	0.3 (0.23–0.52)	< 0.01
WBC	8.95 (7.49–11.95)	5.9 (4.86–7.67)	< 0.01
Hb	113 (97–131)	129 (117–140)	< 0.01
PLT	336 (264–443)	214 (178–264)	< 0.01
ESR	39.5 (23–56)	10 (5–23)	< 0.01
CRP	25.9 (11.7–77)	2.93 (1.73–6.86)	< 0.01

Abbreviations: UC, ulcerative colitis; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; PLT, platelet count; FIB, fibrinogen; FDP, fibrin/fibrinogen degradation products; WBC, white blood cell.

Table 4 Correlations of FIB, FDP, D-Dimer and Inflammatory Index

Parameters	ESR		CRP		PLT	
	r value	P value	r value	P value	r value	P value
FIB	0.81	<0.01	0.805	<0.01	0.483	< 0.01
FDP	0.511	<0.01	0.5	<0.01	0.41	< 0.01
D-dimer	0.644	<0.01	0.656	<0.01	0.5	< 0.01

Note: P and r values were estimated using Spearman correlation analysis.
Abbreviations: ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; PLT, platelet count; FIB, fibrinogen; FDP, fibrin/fibrinogen degradation products.

Correlation Analysis

Positive correlations were observed between FIB level and ESR ($r = 0.81$, $p < 0.01$), CRP level ($r = 0.8$, $p < 0.01$), and PLT level ($r = 0.483$, $p < 0.01$). FDP levels were positively associated with ESR ($r = 0.511$, $p < 0.01$), CRP levels ($r = 0.5$, $p < 0.01$), and PLT levels ($r = 0.41$, $p < 0.01$) (Table 4).

ROC Analysis

ROC analysis was used to assess performance of coagulation parameters in discriminating severe UC from non-severe patients. The area under the curve (AUC) of D-dimer was 0.852 (95% CI, 0.805–0.898), and the optimum cut-off point was 0.585, with a sensitivity of 80.6% and specificity of 78.9%. The AUC of FIB was 0.853 (95% CI, 0.807–0.9) and the AUC of FDP was 0.801 (95% CI, 0.741–0.862)(Figure 1). ROC analysis was also plotted for ESR, CRP, and PLT levels, as shown in Table 5.

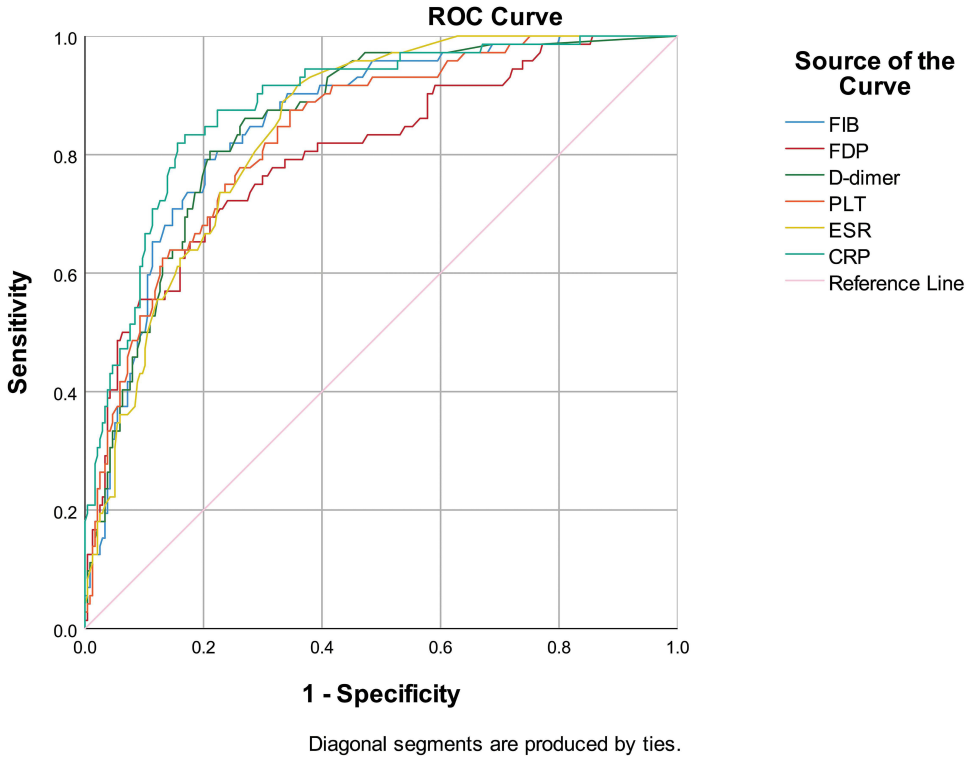

Figure 1 Receiver operating characteristic curves of FIB, FDP, D-dimer and inflammatory indexes in differentiating severe from non-severe UC patients.
Abbreviations: ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; PLT, platelet count; FIB, fibrinogen; FDP, fibrin/fibrinogen degradation products; ROC: Receiver operator characteristic.

Table 5 The Diagnostic Value of of FIB, FDP, D-Dimer and Inflammatory Indexes

Parameters	AUC	SE	Lower limit	Upper limit
FIB	0.853	0.024	0.807	0.9
FDP	0.801	0.031	0.741	0.862
D-dimer	0.852	0.024	0.805	0.898
ESR	0.842	0.023	0.798	0.887
CRP	0.884	0.022	0.841	0.927
PLT	0.836	0.025	0.787	0.886

Abbreviations: ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; PLT, platelet count; FIB, fibrinogen; FDP, fibrin/fibrinogen degradation products; AUC, area under the curve; SE, Standard error.

Discussion

The increased risk of thromboembolic events in patients with UC has received increasing attention. Consensus guidelines recommend anticoagulant prophylaxis for patients with severe UC.[21] Biomarkers have been explored to evaluate UC severity.[19] ESR and CRP are considered reliable markers of disease activity. However, the diagnostic performance of conventional biomarkers remains not optimal. Coagulation abnormalities have also been detected in UC patients. Our study aimed to evaluate the coagulation parameters in UC patients.

In this retrospective study of 364 patients, severe UC was associated with higher D-dimer, FDP, and FIB levels. We also found that coagulation parameters positively correlated with conventional inflammatory indicators. This result is consistent with the majority of previous data supporting hypercoagulation status in UC. Bai et al included 50 patients with UC and reported that UC patients had higher levels of D-dimer.[22] Similarly, a Chinese retrospective study showed D-dimer levels were higher in patients with UC than in healthy subjects.[23] Xu et al enrolled 29 patients with UC and found active UC had a higher D-dimer than inactive disease.[24] However, a study including 38 active UC patients and 13 quiescent UC patients reported no significant differences in plasma D-dimer levels between active and inactive UC.[25] A retrospective study including 108 CD patients indicated no differences in D-dimer levels between low and high disease activity CD patients.[26]

Our study found elevated plasma fibrinogen levels in the patients with severe UC. This finding is supported by other studies. Chen et al enrolled 788 patients with IBD and found significantly elevated fibrinogen levels. The AUC for fibrinogen was 0.806 (95% CI: 0.751–0.861). The optimum cut-off point of fibrinogen was 3.22 for active UC.[27] However, Banait et al conducted a study that included 86 patients with UC and found no significant difference in fibrinogen levels between patients with active UC and those in remission.[28] Similarly, another retrospective study did not find a significant difference in FIB levels between UC patients and healthy controls.[23]

Other inflammatory markers such as CRP, ESR, and PLT were also evaluated in the present study. We observed a positive correlation among D-dimer, FDP, FIB, and conventional biomarkers. In this study, the AUC for CRP and ESR were (0.884, 95% CI: 0.841–0.927) and (0.842, 95% CI: 0.798–0.887), respectively. FIB and D-dimer were less effective than CRP, but were superior to ESR in differentiating severe from non-severe UC.

Some studies showed D-dimer values on admission are useful factors for predicting venous thromboembolic events in patients with UC.[29,30] The pathogenesis of VTE is not clearly understood. Possible mechanisms include the activation of the coagulation cascade, endothelial dysfunction, and disturbed fibrinolysis. Inflammation and coagulation are closely related.[31–33] Several studies have indicated that tumor necrosis factor-alpha, interleukin-6, and cytokines contribute to coagulation activation. Our previous study showed that plasma IL-6 levels were elevated in patients with active UC.[34] Abnormalities in platelets appear to be associated with the risk of VTE. Platelets have been reported to regulate coagulation and inflammation.[31] Our study observed higher D-dimer and platelet levels in patients with severe UC than non-severe group.

Glucocorticoids and biologics have been reported to affect the coagulation states. Recent study showed significantly higher risk of venous thromboembolism in patients treated with steroid.[35] Due to its anti-inflammatory properties, biologics have been reported to play a protective role in thromboembolism. There are limited data on the association between biologics and risk of thrombosis.[36] However, case reports showed UC patients develop VTE when receiving tofacitinib.[37] A meta analysis involving 58518 IBD patients suggested that steroid but not biologic agents increased the risk of VTE.[38] In our study, only a few patients were under biologic therapy. Therefore, we did not assess the effect of biologics or steroid on the coagulation parameters.

Our study had some limitations. Data were extracted from the medical records. This includes the inherent limitations of retrospective studies. Firstly, the sample size is relatively small. Secondly, we were unable to evaluate other variables such as surgery, central venous catheters, smoking, and oral contraceptives.[6,39] Another limitation is that disease severity was determined according to Truelove and Witts criteria. Endoscopy was not performed in some patients. We are unable to evaluate endoscopic activity and histopathology data.

In conclusion, this study showed that FIB, FDP, and D-dimer levels can be useful for differentiating severe from non-severe UC. Coagulation parameters are potential biomarkers for monitoring disease activity. Further prospective studies are required to evaluate the characteristics of coagulation alterations in UC patients.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Nanjing TCM University. Informed consent was waived because of retrospective design. During the study, patient data confidentiality and compliance with the Declaration of Helsinki were followed.

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Disclosure

The authors declare that they have no competing interests.

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