

Impaired Coagulation Status in the Crohn's Disease Patients Complicated with Intestinal Fistula

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Abstract

Background: Intestinal fistula is one of the common complications of Crohn's disease (CD) that might require surgical treatment. The clinical characteristics and outcomes of CD with intestinal fistula are much different from CD alone. This study was to investigate whether the coagulation status of CD is changed by intestinal fistula.

Methods: Data were retrospectively analyzed for 190 patients with a definitive diagnosis of CD who were registered at the Jinling Hospital between January 2014 and September 2015. Baseline clinical characteristics and laboratory indices of initial admission and 7 days after intestinal fistula resections were collected. Student's *t*-test and the Wilcoxon rank-sum test were used to compare differences between the two groups.

Results: Compared with CD patients without intestinal fistula, prothrombin time (PT) in patients with intestinal fistula was significantly longer (12.13 ± 1.27 s vs. 13.18 ± 1.51 s, $P < 0.001$ in overall cohort; 11.56 ± 1.21 s vs. 12.61 ± 0.73 s, $P = 0.001$ in females; and 12.51 ± 1.17 s vs. 13.37 ± 1.66 s, $P = 0.003$ in males). Platelet (PLT) count was much lower in intestinal fistula group than in nonintestinal fistula group ($262.53 \pm 94.36 \times 10^9/L$ vs. $310.36 \pm 131.91 \times 10^9/L$, $P = 0.009$). Multivariate logistic regression showed that intestinal fistula was significantly associated with a prolonged PT (odds ratio [OR] = 1.900, $P < 0.001$), a reduced amount of PLT ($OR = 0.996$, $P = 0.024$), and an increased operation history ($OR = 5.408$, $P < 0.001$). Among 65 CD patients receiving intestinal fistula resections, PT was obviously shorter after operation than baseline (12.28 ± 1.16 s vs. 13.02 ± 1.64 s, $P = 0.006$).

Conclusions: Intestinal fistula was significantly associated with impaired coagulation status in patients complicated with CD. Coagulation status could be improved after intestinal fistula resections.

Key words: Coagulation; Crohn's Disease; Inflammatory Bowel Disease; Intestinal Fistula; Prothrombin Time

INTRODUCTION

Crohn's disease (CD) is a form of inflammatory bowel disease (IBD), which mainly involves the end of the small intestine and beginning of the colon.^[1] The clinical manifestations and complications of CD are complex and varied, and they make CD challenging for both patients and physicians. There have been several controversies in the coagulation status of CD. In most studies, a hypercoagulable coagulation status was present in CD patients, resulting in high risk of venous thromboembolism (VTE).^[2] However, other study has reported that prothrombin time (PT) was significantly higher in CD patients than in healthy controls.^[3]

Increasing amounts of research suggested that inflammation and coagulation were closely related and had interaction

effects.^[4-7] In some severe infectious events, such as intestinal fistula, the coagulation state is mainly hypocoagulable.^[8] Intestinal fistula is one of the common complications of CD. Because of intestinal fistula often along with abdominal infection and malnutrition, the clinical characteristics and outcomes of such patients are much different from those of patients with CD alone. Hence, the coagulation status of CD

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patients complicated with intestinal fistula possibly differs from that of the simple CD patients.

It is essential for CD patients who require surgical intervention, for example, CD patients complicated with intestinal fistula, to monitor their coagulation status regularly and systematically. Normal coagulation status is closely related to a favorable prognosis and offers the safety of subsequent operations. This study aimed to evaluate abnormalities in coagulation in CD patients complicated with intestinal fistula and to investigate whether the coagulation status changed is associated with intestinal fistula of CD.

METHODS

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Jinling Hospital. Informed consent was obtained from all patients via telephone before their enrollment in this study.

Patients

Data were retrospectively analyzed for 190 patients with a definitive diagnosis of CD, who were registered in the Department of General Surgery at Jinling Hospital between January 2014 and September 2015. A definitive diagnosis of CD was based on the results of multiple examinations, such as colonoscopy, small bowel capsule endoscopy, enteroscopy, gastroscopy, computed tomography, enterography, histopathological examination, and blood tests (including routine blood examination, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and autoimmune-related antibodies). Overall, 31 patients were excluded from this study, including 20 who did not undergo coagulation function tests, eight who had received blood transfusions or hemostatic drugs, and three who were under 16 years of age when they were diagnosed.

The patients' data were collected from the electronic database at Jinling Hospital. The data included gender, age, smoking status (yes or no), regular rest (yes or no, meaning that work and rest times were relatively fixed), body mass index (BMI), disease locations (small bowel only, colon only, or small bowel and colon), operation history (ileocecal resection, other small bowel resection, or colon resection), intestinal fistula (yes or no, meaning that the patient had complications of CD that needed surgical intervention), and current medication (mesalazine, sulfasalazine, or azathioprine).

The study group was stratified by complicated with or without intestinal fistula. The diagnosis of intestinal fistula was made by the findings of sonography, abdominal CT, barium meal or enema, and enteroscopy or colonoscopy. All the fistulas included were enterocutaneous fistulas. Each group was stratified by gender because there are differences between clinical manifestations of CD and coagulation function in males and females. Demographics, clinical characteristics, and initial admission laboratory indices were compared between groups and subgroups.

Blood samples

After initial admission to the hospital and 7 days after intestinal fistula resections (only performed in the postoperative patients), early morning fasting venous blood samples were obtained from each patient after a 12-h fast. Laboratory indices were tested, including CRP, ESR, platelets (PLTs), mean platelet volume (MPV), PT, fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT), and international normalized ratio (INR). All of the samples were analyzed in duplicate at the Department of Clinical Laboratory, Jinling Hospital.

Statistical analysis

All statistical analyses were performed using the statistical software SPSS Statistics Version 20.0 (IBM, Chicago, IL, USA). Categorical variables were presented as a percentage of the total. Quantitative variables were summarized as mean \pm standard deviation (SD). Student's *t*-test (for numerical data) and the Wilcoxon rank-sum test (for nonparametric data) were used to compare differences between the two groups. Differences in the frequencies for categorical data were compared using the Chi-square test or Fisher's exact test in the case of a small sample size ($n < 5$ per group). Multivariate logistic regression analyses were performed to determine the variables associated with complications, and odds ratios (ORs) were estimated with the associated *P* values. A $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline clinical characteristics of the overall study group

Baseline clinical characteristics of the overall study group are shown in Table 1. A significant difference could be observed in gender distribution between intestinal fistula and nonintestinal fistula groups (female: 26.0% vs. 43.0%, $P = 0.025$). There was no significant difference in age, smoking status, regular rest, BMI, disease locations, or current medication between the two groups (all $P > 0.05$). A higher rate of operation history was discovered in the intestinal fistula group (58.9%) than that of the nonintestinal fistula group (25.6%, $P < 0.001$), especially for other small bowel resection (31.5% vs. 17.4%, $P = 0.038$) and colon resection (20.5% vs. 3.5%, $P = 0.001$).

As shown in Table 1, PT in intestinal fistula group (13.18 ± 1.51 s) was significantly longer than that of nonintestinal fistula group (12.13 ± 1.27 s, $P < 0.001$). Similarly, APTT was markedly longer (35.91 ± 9.95 s vs. 32.75 ± 6.08 s, $P = 0.019$) and INR was higher (1.17 ± 0.24 vs. 1.05 ± 0.11 , $P < 0.001$) in intestinal fistula group, compared with nonintestinal fistula group. In addition, PLT count in intestinal fistula group was much lower than that of nonintestinal fistula group ($[262.53 \pm 94.36] \times 10^9/L$ vs. $[310.36 \pm 131.91] \times 10^9/L$, $P = 0.009$). There was no significant difference in CRP, ESR, MPV, FIB, and TT between the two groups.

Table 1: Baseline and clinical characteristics of the overall study group

Characteristics	Intestinal fistula group (n = 73)	Nonintestinal fistula group (n = 86)	Statistical values	P
Female	19 (26.0)	37 (43.0)	4.999 [†]	0.025
Age (years)	35.6 ± 12.7	32.4 ± 11.7	1.685	0.094
Smoker	16 (21.9)	17 (19.8)	0.111 [†]	0.739
Regular rest	71 (97.3)	83 (96.5)	0.073 [†]	1.000
BMI (kg/m ²)	18.5 ± 2.7	18.2 ± 2.9	0.500	0.618
Disease locations				
Only small bowel	36 (49.3)	35 (40.7)	1.186 [†]	0.276
Only colon	13 (17.8)	22 (25.6)	1.390 [†]	0.238
Small bowel and colon	24 (32.9)	29 (33.7)	0.013 [†]	0.910
Operation history*	43 (58.9)	22 (25.6)	18.141 [†]	<0.001
Ileocecal resection	17 (23.3)	10 (11.6)	3.808 [†]	0.051
Other small bowel resection	23 (31.5)	15 (17.4)	4.295 [†]	0.038
Colon resection	15 (20.5)	3 (3.5)	11.446 [†]	0.001
Current medication				
Mesalazine	15 (20.5)	10 (11.6)	2.371 [†]	0.124
Sulfasalazine	4 (5.5)	3 (3.5)	0.372 [†]	1.000
Laboratory indexes of initial admission				
CRP (mg/L)	42.17 ± 58.56	27.81 ± 42.71	1.727	0.087
ESR (mm/h)	29.06 ± 24.06	25.88 ± 23.73	0.746	0.457
PLT (×10 ⁹ /L)	262.53 ± 94.36	310.36 ± 131.91	-2.646	0.009
MPV (fl)	9.53 ± 1.58	9.15 ± 1.41	1.626	0.106
PT (s)	13.18 ± 1.51	12.13 ± 1.27	4.619	<0.001
FIB (g/L)	3.61 ± 1.05	3.50 ± 1.07	0.607	0.545
APTT (s)	35.91 ± 9.95	32.75 ± 6.08	2.374	0.019
TT (s)	17.67 ± 1.79	17.50 ± 1.50	0.605	0.546
INR	1.17 ± 0.24	1.05 ± 0.11	3.809	<0.001

Data are shown as n (%) or mean ± SD. *As a patient may have undergone several operations, the percentage totals more than 100%. [†]Wilcoxon rank-sum test, otherwise Student's *t*-test. BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PLT: Platelet; MPV: Mean platelet volume; PT: Prothrombin time; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; SD: Standard deviation.

Clinical characteristics of the study subgroups stratified by gender

No significant differences were found in age, regular rest, BMI, disease locations, current medication, or some laboratory indexes (such as CRP, ESR, FIB, and TT) between two subgroups of females and males.

In females, intestinal fistula subgroup tended to have more operation history than nonintestinal fistula subgroup (52.6% vs. 18.9%, *P* = 0.009). The PT in intestinal fistula group (12.61 ± 0.73 s) was significantly longer than that in nonintestinal fistula subgroup (11.56 ± 1.21 s, *P* = 0.001). Similarly, INR was higher in intestinal fistula subgroup, compared with nonintestinal fistula subgroup (1.19 ± 0.41 vs. 1.01 ± 0.10, *P* = 0.021). In addition, MPV was also higher in intestinal fistula subgroup (10.13 ± 1.77 fl vs. 8.80 ± 1.39 fl, *P* = 0.003; Table 2).

In males, intestinal fistula subgroup also tended to have more operation history than nonintestinal fistula subgroup (61.1% vs. 30.6%, *P* = 0.002). Moreover, patients in intestinal fistula subgroup had more colon resection (24.1% vs. 2.0%, *P* = 0.001), which was not consistent with results in females. PT in intestinal fistula subgroup (13.37 ± 1.66 s) was significantly longer than that of nonintestinal fistula subgroup (12.51 ± 1.17 s, *P* = 0.003).

Similarly, compared with nonintestinal fistula subgroup, APTT was longer (33.39 ± 5.52 s vs. 37.01 ± 10.91 s, *P* = 0.042) and INR was higher (1.09 ± 0.99 vs. 1.16 ± 0.14, *P* = 0.003) in intestinal fistula subgroup. Furthermore, PLT count was lower in intestinal fistula subgroup ([268.59 ± 97.96] × 10⁹/L vs. [321.55 ± 142.92] × 10⁹/L, *P* = 0.029; Table 3).

Impact of intestinal fistula on coagulation status of Crohn's disease patients

As shown in Table 4, multivariate logistic regression showed that in the overall cohort, intestinal fistula was significantly associated with a prolonged PT (*OR* = 1.900, *P* < 0.001), a reduced amount of PLT (*OR* = 0.996, *P* = 0.024), and an increased operation history (*OR* = 5.408, *P* < 0.001). In females, intestinal fistula was also significantly associated with a prolonged PT (*OR* = 2.727, *P* = 0.014) and an increased operation history (*OR* = 5.360, *P* < 0.001). Besides that, intestinal fistula was associated with an elevated MPV (*OR* = 1.680, *P* = 0.039). In males, intestinal fistula was significantly associated with a reduced amount of PLT (*OR* = 0.996, *P* = 0.048), an increased operation history (*OR* = 5.256, *P* = 0.007), and an elevated INR (*OR* = 717.273, *P* = 0.003).

Table 2: Baseline and clinical characteristics of the female CD patients with or without intestinal fistula

Characteristics	Intestinal fistula female subgroup (n = 19)	Nonintestinal fistula female subgroup (n = 37)	Statistical values	P
Age (years)	40.5 ± 14.7	35.9 ± 12.8	1.214 [†]	0.230
Regular rest	19 (100.0)	36 (97.3)	0.523	1.000
BMI (kg/m ²)	18.6 ± 2.9	17.8 ± 2.6	0.885 [†]	0.381
Disease locations				
Only small bowel	11 (57.9)	14 (37.8)	2.043	0.153
Only colon	2 (10.5)	13 (35.1)	3.877	0.061
Small bowel and colon	6 (31.6)	10 (27.0)	0.127	0.721
Operation history*	10 (52.6)	7 (18.9)	6.749	0.009
Ileocecal resection	5 (26.3)	3 (8.1)	3.399	0.105
Other small bowel resection	4 (21.1)	3 (8.1)	1.923	0.212
Colon resection	2 (10.5)	2 (5.4)	0.496	0.598
Current medication				
Mesalazine	3 (15.8)	2 (5.4)	1.665	0.324
Sulfasalazine	1 (5.3)	0 (0)	1.983	0.339
Laboratory indexes of initial admission				
CRP (mg/L)	32.76 ± 49.27	21.77 ± 35.52	0.952 [†]	0.345
ESR (mm/h)	32.87 ± 22.18	27.24 ± 23.40	0.769 [†]	0.446
PLT (×10 ⁹ /L)	245.32 ± 83.30	295.14 ± 115.46	-1.663 [†]	0.102
MPV (fl)	10.13 ± 1.77	8.80 ± 1.39	3.064 [†]	0.003
PT (s)	12.61 ± 0.73	11.56 ± 1.21	3.404 [†]	0.001
FIB (g/L)	3.64 ± 0.97	3.23 ± 1.00	1.415 [†]	0.164
APTT (s)	32.79 ± 5.67	31.78 ± 6.81	0.542 [†]	0.590
TT (s)	17.78 ± 1.63	17.81 ± 1.13	-0.148 [†]	0.955
INR	1.19 ± 0.41	1.01 ± 0.10	0.099 [†]	0.021

Data are shown as n (%) or mean ± SD. *As a patient may have undergone several operations, the percentage totals more than 100%. [†]Student's *t*-test, otherwise Wilcoxon rank-sum test. BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PLT: Platelet; MPV: Mean platelet volume; PT: Prothrombin time; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; SD: Standard deviation; CD: Crohn's disease.

Comparisons of coagulation status in Crohn's disease patients before and after intestinal fistula resection

Sixty-five patients received intestinal fistula resections and their coagulation status before and after operation was compared. As shown in Table 5, compared with the baseline, the patients showed shorter PT (13.02 ± 1.64 s vs. 12.28 ± 1.16 s, $P = 0.006$), lower INR (1.13 ± 0.14 vs. 1.08 ± 0.10 , $P = 0.003$), lower PLT count ($[256.70 \pm 82.47] \times 10^9/L$ vs. $[221.81 \pm 101.28] \times 10^9/L$, $P = 0.004$), more MPV (9.59 ± 1.59 fl vs. 10.06 ± 1.40 fl, $P = 0.003$), more FIB (3.37 ± 1.18 g/L vs. 3.92 ± 1.02 g/L, $P = 0.009$), and shorter TT (17.92 ± 1.96 s vs. 17.18 ± 1.86 s, $P = 0.044$) after intestinal fistula resections.

DISCUSSION

This study evaluated the impact of intestinal fistula on coagulation status in CD patients. PT in patients with intestinal fistula was significantly longer than patients without intestinal fistula in the overall cohort, females and males. Meanwhile, INR was higher in the overall intestinal fistula group and the corresponding subgroups. The blood PLT counts were less in the overall intestinal fistula group and the corresponding male group. With no doubt, patients with intestinal fistula also tended to have more operation history, no matter in females or in males. Logistic regression

analysis identified that, in the overall cohort, intestinal fistula was significantly associated with prolonged PT, decreased amount of PLT, and increased operation history. In females, intestinal fistula was significantly associated with prolonged PT and increased operation history. In males, intestinal fistula was significantly associated with elevated INR, increased operation history, and decreased amount of PLT.

Intestinal fistula is one of the common complications of CD, and most patients are likely to need further surgery. Hence, it is critical to recognize accurately the coagulation status of CD patients complicated with intestinal fistula. Previous studies mainly focused on the coagulation state of CD patients without intestinal fistula, and most conclusions were that CD patients tended to have a hypercoagulable coagulation status, and the risk of VTE in CD patients was increased,^[2] as reported by Alatri *et al.* in 2016.^[9] The incidence of VTE in CD patients was not common (approximately 1–8%); however, it was a two- to four-fold higher risk of VTE than healthy people.^[10] A meta-analysis showed that the risks of VTE were similar in patients with ulcerative colitis and CD.^[11] What's more, the American Gastroenterological Association^[12,13] and the European Crohn's and Colitis Organization^[14] recommended the prophylactic use of low-molecular-weight heparin in CD patients with active disease to avoid the risk of VTE.

Table 3: Baseline and clinical characteristics of the male CD patients with or without intestinal fistula

Characteristics	Intestinal fistula male subgroup (n = 54)	Nonintestinal fistula male subgroup (n = 49)	Statistical values	P
Age (years)	33.9 ± 11.6	29.7 ± 10.2	1.949 [†]	0.054
Smoker	16 (29.6)	17 (34.7)	0.303	0.582
Regular rest	52 (96.3)	47 (95.9)	0.010	1.000
BMI (kg/m ²)	18.5 ± 2.6	18.6 ± 3.1	-0.191 [†]	0.849
Disease locations				
Only small bowel	25 (46.3)	21 (42.9)	0.123	0.726
Only colon	11 (20.4)	9 (18.4)	0.066	0.797
Small bowel and colon	18 (33.3)	19 (38.8)	0.331	0.565
Operation history*	33 (61.1)	15 (30.6)	9.603	0.002
Ileocecal resection	12 (22.2)	7 (14.3)	1.076	0.300
Other small bowel resection	19 (35.2)	12 (24.5)	1.397	0.237
Colon resection	13 (24.1)	1 (2.0)	10.619	0.001
Current medication				
Mesalazine	12 (22.2)	8 (16.3)	0.571	0.450
Sulfasalazine	3 (5.6)	3 (6.1)	0.015	1.000
Laboratory indexes of initial admission				
CRP (mg/L)	45.54 ± 61.63	32.26 ± 47.16	1.215 [†]	0.227
ESR (mm/h)	27.59 ± 24.86	25.02 ± 24.15	0.482 [†]	0.631
PLT (×10 ⁹ /L)	268.59 ± 97.96	321.55 ± 142.92	-2.211 [†]	0.029
MPV (fl)	9.32 ± 1.47	9.40 ± 1.37	-0.284 [†]	0.777
PT (s)	13.37 ± 1.66	12.51 ± 1.17	3.065 [†]	0.003
FIB (g/L)	3.60 ± 1.08	3.68 ± 1.08	-0.394 [†]	0.694
APTT (s)	37.01 ± 10.91	33.39 ± 5.52	2.058 [†]	0.042
TT (s)	17.62 ± 1.85	17.30 ± 1.68	0.904 [†]	0.368
INR	1.16 ± 0.14	1.09 ± 0.99	3.101 [†]	0.003

Data are shown as n (%) or mean ± SD. *As a patient may have undergone several operations, the percentage totals more than 100%. [†]Student's *t*-test, otherwise Wilcoxon rank-sum test. BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PLT: Platelet; MPV: Mean platelet volume; PT: Prothrombin time; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; SD: Standard deviation; CD: Crohn's disease.

PT in most patients complicated with intestinal fistula had prolonged PT in this study, and prolonged PT remained within the normal limits (12.61 ± 0.73 s in females, 13.37 ± 1.66 s in males). No serious coagulation disorders occurred during the research period. However, if coumarins, for example, warfarin, were prescribed for CD patients with intestinal fistula, impaired coagulation status would be aggravated. Therefore, the recommendations of guidelines about low-molecular-weight heparin were quite reasonable, and serious complications related to abnormal coagulation could be avoided as possible. We conducted this research to raise physicians' awareness about following the recommendations of guidelines and choosing the right coagulation-related medicine for CD patients with intestinal fistula.

Previous studies showed that administration of drugs may affect the coagulation status. For example, corticosteroids were confirmed to be associated with both hypocoagulation and hypercoagulation changes,^[15] and 5-aminosalicylic acid significantly reduced both spontaneous and thrombin-induced PLT activation.^[16] However, as there was no difference in drug use in the two groups, the impact of medications on changes in coagulation could be excluded in our study.

The ileum is an important site for Vitamin K absorption in humans,^[17] and ileal lesions are common in patients with

Table 4: Multivariate logistic regression analysis of risk factors for intestinal fistula of CD

Factors	Intestinal fistula		
	OR	95% confidence interval	P
Total			
Gender	0.995	0.423–2.342	0.990
Operation history	5.408	2.372–11.148	<0.001
PLT	0.996	0.993–0.999	0.024
PT	1.900	1.379–2.617	<0.001
APTT	0.992	0.929–1.059	0.816
INR	11.710	–	0.788
Female			
Operation history	5.360	1.296–29.603	<0.001
MPV	1.680	1.025–2.752	0.039
PT	2.727	1.229–6.048	0.014
INR	7.828	–	0.905
Male			
Operation history	5.256	1.795–11.344	0.007
PLT	0.996	0.992–1.000	0.048
PT	0.766	–	0.951
APTT	1.029	0.951–1.113	0.480
INR	717.273	–	0.003

PLT: Platelet; MPV: Mean platelet volume; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; –: Not applicable; OR: Odds ratio; CD: Crohn's disease.

Table 5: Coagulation status in 65 CD patients before and after intestinal fistula resection

Laboratory indexes	Before operation	After operation	<i>t</i>	<i>P</i>
CRP (mg/L)	36.15 ± 61.88	34.62 ± 35.77	0.166	0.869
PLT (×10 ⁹ /L)	256.70 ± 82.47	221.81 ± 101.28	3.018	0.004
MPV (fl)	9.59 ± 1.59	10.06 ± 1.40	-3.076	0.003
PT (s)	13.02 ± 1.64	12.28 ± 1.16	2.884	0.006
FIB (g/L)	3.37 ± 1.18	3.92 ± 1.02	-2.757	0.009
APTT (s)	36.51 ± 11.33	35.72 ± 5.64	0.442	0.661
TT (s)	17.92 ± 1.96	17.18 ± 1.86	2.076	0.044
INR	1.13 ± 0.14	1.08 ± 0.10	3.146	0.003

Data are shown as mean ± SD. CRP: C-reactive protein; PLT: Platelet; MPV: Mean platelet volume; PT: Prothrombin time; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; CD: Crohn's disease; SD: Standard deviation.

CD.^[1] In this study, ileal lesions were present in most of the CD patients (44.7%). Vitamin K deficiency can result in a decrease in prothrombin (Factor II), Factor VII, Factor IX, and Factor X,^[18] which causes prolonged PT. In regard to the Vitamin K deficiency, it was a limit of this study due to the nature of retrospective study. The Vitamin K levels were not included in the database of CD patients. However, for the patients with risk of hemorrhage or being suspected of Vitamin K deficiency, prophylactic Vitamin K1 was commonly prescribed in our department (10 mg/d). In addition, 10 mg/d Vitamin K1 was a safe dose, which was proved by previous research.^[19] Further prospective research about Vitamin K deficiency in CD patients should be done in the future.

The decrease in Factor V and FIB is also associated with the coagulation function of CD. However, the study has shown that there were no significant differences in Factor V^[20] between patients with CD and controls.^[21] FIB levels in CD patients (4.91 g/L) were significantly higher than that of the control group (2.55 g/L, $P < 0.05$). The PT might be prolonged as a result of disseminated intravascular coagulation (DIC). However, all patients were checked, and none of them had a diagnosis of DIC.

Nguyen and Sam^[22] reported that intestinal fistula was independently associated with a greater VTE risk. However, in the present study, intestinal fistula was significantly associated with prolonged PT. Nguyen and Sam^[22] did not show BMI data. The BMI of CD patients in the Western population was reported as $24.7 \pm 4.3 \text{ kg/m}^2$,^[23] which was higher than that of our study. A higher BMI was confirmed to be related to a greater VTE risk.^[24] This might partially explain the contradictory findings. Based on the previous research, the clinical manifestations of CD were notable in ethnic differences. Wang *et al.*^[25] reported that the PT in Chinese CD patients was significantly longer than healthy controls. Shen *et al.*^[3] also reported that PT in Chinese female CD patients was markedly longer than that of healthy controls. A study from Turkey^[20] also showed that PT in active IBD was longer than that in controls ($12.5 \pm 1.2 \text{ s}$ vs. $11.5 \pm 0.7 \text{ s}$, $P < 0.05$). There are also ethnic variations in coagulation status. The risk of VTE was reported to be significantly lower in the East Asian cohorts, such as Chinese and Japanese.^[26] The above conclusions are opposite of those presented in most Western research. Thus, their location and ethnic variations in patients

with CD should not be ignored, and this may require further research and analysis.

The impact of inflammation on coagulation status has been investigated in several studies, which showed that an inflammatory mechanism shifted the hemostatic balance to favor activation of coagulation.^[4-7,27] Despite there were no significant differences in CRP between groups and corresponding subgroups, in intestinal fistula group, PT correlated significantly with CRP (Pearson's $r = 0.382$, $P = 0.001$). This result verified the revealed relationships between inflammation and coagulation at some level. Nevertheless, the impact of inflammation on coagulation is complex and it remains unclear. The change in the coagulation status in CD patients complicated with intestinal fistula still cannot be confirmed by existing research.

For the patients who received intestinal fistula resections in our center, PT was obviously shorter after surgery. In the meanwhile, other indexes of coagulation status, such as PLT count, MPV, INR, FIB, and TT, were also changed. That meant that coagulation status was improved to some extent. However, the postoperative coagulation status was only explored in a short period (7 days) after surgery. Long-term follow-up would be conducted to explore the trends of changes in postoperative coagulation status in the future study.

Our study had some limitations. The data for some patients were incomplete. Therefore, statistical bias related to the missing data might be existed in this study. In addition, the patients were recruited from a single center and the sample size was small. Finally, because of the study's retrospective design, there was a potential risk of selection bias. Thus, our results might not completely reflect the impact of intestinal fistula on coagulation status in CD patients. Large-scale prospective multicenter clinical studies are needed to further confirm our conclusions.

In conclusion, intestinal fistula was significantly associated with impaired coagulation status in patients complicated with CD. Coagulation status could be improved after intestinal fistula resections.

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Conflicts of interest

There are no conflicts of interest.

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克罗恩病合并肠瘘患者的凝血功能障碍

摘要

背景: 肠瘘是克罗恩病的常见并发症之一,可能需要手术处理。合并有肠瘘的克罗恩病在临床特征和预后上,与未合并肠瘘的克罗恩病相比差异较大。本研究是为了探究克罗恩病的凝血功能是否会因伴有肠瘘而改变。

方法: 2014年1月至2015年9月,南京大学附属金陵医院普通外科收治的190名确诊克罗恩病的患者入组。收集入院时和肠瘘切除术后第7天的临床资料及实验室指标。利用t检验和秩和检验比较组间差异。

结果: 与未合并肠瘘的克罗恩病患者相比,合并肠瘘的克罗恩病患者的凝血酶原时间明显延长(所有患者: 12.13 ± 1.27 秒 vs. 13.18 ± 1.51 秒, $P < 0.001$; 女性亚组: 11.56 ± 1.21 秒 vs. 12.61 ± 0.73 秒, $P = 0.001$; 男性亚组: 12.51 ± 1.17 秒 vs. 13.37 ± 1.66 秒, $P = 0.003$)。肠瘘组的小板计数明显低于非肠瘘组 ($262.53 \pm 94.36 \times 10^9/L$ vs. $310.36 \pm 131.91 \times 10^9/L$, $P = 0.009$)。多因素回归分析发现肠瘘与凝血酶原时间延长($OR = 1.900$, $P = 0.000$),血小板计数增加($OR = 0.996$, $P = 0.024$)和手术史增多($OR = 5.408$, $P < 0.001$)相关。在65名接受肠瘘切除手术的克罗恩病患者中,术后凝血酶原时间较术前明显缩短(12.28 ± 1.16 秒 vs. 13.02 ± 1.64 秒, $P = 0.006$)。

结论: 克罗恩病患者合并的肠瘘与其凝血功能障碍显著相关,凝血功能可在肠瘘切除术后改善。