Correlation of D-dimer level with the inflammatory conditions: a retrospective study

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Background: D-dimer is produced during the fibrinolysis. A retrospective study was conducted to assess the association between D-dimer and inflammatory parameters in unselected patients with digestive diseases. **Methods:** All patients who were consecutively admitted to our department between January 2016 and October 2016 and underwent D-dimer tests were included. Spearman non-parametric tests and Pearson chi-square tests were performed to evaluate the correlation of D-dimer with inflammatory parameters. The correlation coefficients were calculated.

Results: Overall, 205 patients (112 males and 93 females) underwent 245 D-dimer tests. Among them, 9 patients were diagnosed with pancreatitis (8 males and 1 female) and 14 patients with liver cirrhosis (6 males and 8 females). In the overall analysis, D-dimer positively correlated with white blood cell (WBC), percentage of neutrophils, neutrophil count, C reaction protein, high sensitive C reaction protein (hsCRP), procalcitonin (PCT), and blood culture detection, but negatively correlated with lymphocyte percentage and lymphocyte count. In the subgroup analysis of patients with pancreatitis, D-dimer positively correlated with hsCRP and PCT. In the subgroup analysis of patients with liver cirrhosis, D-dimer positively correlated with WBC and hsCRP.

Conclusions: D-dimer may reflect the inflammation conditions in unselected patients with digestive diseases. Further validation study should focus on the patients with specific digestive diseases.

Keywords: D-dimer; inflammation; digestive diseases; correlation; cirrhosis; pancreas

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Introduction

D-dimer is a specific metabolite of cross-linked fibrin formed by plasma fibrinolytic enzyme (1). An increased concentration of D-dimer reflects the secondary fibrinolysis. D-dimer has been used in the diagnosis and evaluation of lower extremity deep venous thrombosis (DVT), pulmonary

embolism (PE), disseminated intravascular coagulation (DIC), surgical trauma, and malignant tumors (2).

At present, D-dimer has been widely used in the diagnosis and evaluation of digestive diseases. First, D-dimer might be a predictor of asymptomatic metastasis and peritoneal dissemination in patients with gastric cancer (3,4). Also, D-dimer was a prognostic biomarker for metastatic

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gastric cancer treated by chemotherapy (5). Second, plasma D-dimer is a potential biomarker for the diagnosis of portal vein thrombosis (PVT) in patients with cirrhosis (6). Our meta-analysis found that D-dimer might be regarded as a diagnostic marker for PVT in liver cirrhosis. Postoperative D-dimer test is worthwhile for the diagnosis of PVT after portal hypertension-related surgery (7). Third, our previous study also demonstrated that a higher D-dimer level predicted an increased risk of in-hospital death in liver cirrhosis (8). Fourth, D-dimer might be a robust marker for the severity of hyperlipidemia-induced acute pancreatitis (9). Fifth, a combination of D-dimer and peritoneal irritation signs was a reliable negative predictive value for the exclusion of intestinal necrosis (10).

Recently, some researches explored the correlation between D-dimer and severity of inflammation in patients with acute superior mesenteric venous thrombosis. However, D-dimer poorly correlated with white blood cell (WBC) count and C-reactive protein (11). Herein, we conducted a retrospective study to evaluate whether D-dimer reflected the inflammatory conditions in unselected patients with digestive diseases.

Methods

This was a retrospective study. The study was conceived by Xingshun Qi. The study protocol was written by Wenchun Bao and Xingshun Qi and approved by the Medical Ethical Committee of our hospital. The ethical approval number is k (2016) 37. The patient written informed consent was not required. Inclusion criteria were: (I) patients admitted to the first ward of our department and treated by an attending physician (Xingshun Qi) from January 2016 to October 2016; (II) digestive diseases were diagnosed, such as hepatitis, fatty liver, liver cirrhosis, liver cancer, gastritis, gastric cancer, pancreatitis, pancreatic cancer, gastric and duodenal ulcer, colitis, colon cancer, gastrointestinal bleeding, gastric and intestinal polyps, etc.; (III) age and gender were not limited; (IV) D-dimer tests were performed during hospitalization; and (V) regular laboratory data were complete (including routine blood test, liver function, renal function, etc.). Major exclusion criteria were: (I) the diagnosis was unclear; (II) non-digestive diseases were diagnosed; and (III) D-dimer tests were not performed.

Wenchun Bao reviewed the regular clinical and laboratory data from the electronic medical charts of our hospital in the printed case report forms. The clinical and laboratory data collected at the same day when D-dimer levels were detected were as follows: sex, age, fibrinogen (FIB) (g/L), WBC (10°/L), percentage of neutrophils (GR%) (%), neutrophil count (NE) (10°/L), lymphocyte percentage (LY%) (%), lymphocyte count (LY) (10°/L), red blood cell (RBC) (10¹²/L), hemoglobin (HB) (g/L), hematocrit, platelet count (PLT) (10°/L), mean platelet volume (MPV), platelet hematocrit (%) (fL), C reaction protein (CRP) (mg/L), high sensitive C reaction protein (hsCRP) (mg/L), procalcitonin (PCT) (ng/mL), diagnosis of bleeding and thrombus, and major diseases diagnosed at our department.

The normal range of laboratory data included D-dimer (0.01-0.55 mg/L), FIB (2.00-4.00 g/L), WBC $(3.5\times10^9-9.5\times10^9/\text{L})$, GR% (40-75%), NE $(1.8\times10^9-6.3\times10^9/\text{L})$, LY% (20-50%), LY $(1.1\times10^9-3.2\times10^9/\text{L})$, RBC (male) $(4.3\times10^{12}-5.8\times10^{12}/\text{L})$, HB (male) (130-175 g/L), RBC (female) $(3.8\times10^{12}-5.1\times10^{12}/\text{L})$, HB (female) (115-150 g/L), hematocrit (male) (40-50%), hematocrit (female) (35-45%), PLT $(125\times10^9-350\times10^9/\text{L})$, MPV (6-11.5 fL), platelet hematocrit (male) (0.108-0.272%), platelet hematocrit (female) (0.114-0.287%), CRP ($\le 10 \text{ mg/L}$), hsCRP (0-3 mg/L), and PCT (0-0.05 ng/mL).

Statistical analyses were performed by using the SPSS software. Categorical data were expressed as frequencies (percentage). Continuous data were expressed as means with standard deviations and medians with ranges. Spearman non-parametric tests and Pearson chi-square tests were used to evaluate the correlation of D-dimer levels with the abovementioned parameters. The correlation coefficient was calculated. Two-tailed P<0.05 was considered statistically significant.

Results

A total of 226 consecutive patients were considered. And then, 21 patients who did not perform D-dimer tests were excluded. Finally, 205 patients were included (112 males and 93 females). According to the major diseases, 9 patients had a diagnosis of pancreatitis (8 males and 1 female), 14 patients had a diagnosis of liver cirrhosis (6 males and 8 females), 31 patients had a diagnosis of malignancy (21 males and 10 females), 26 patients had a diagnosis of bleeding (18 males and 8 females), and 29 patients had a diagnosis of thrombus (11 males and 18 females).

These patients underwent 245 D-dimer tests. Thus, 245 groups of data were included in the correlation analysis (*Table 1*).

Correlation of D-dimer with clinical and laboratory data in all patients was shown in *Table 2*. Pearson chi-square AME Medical Journal, 2017 Page 3 of 8

Table 1 Characteristics of data at the time of D-dimer tests

Variables	No. groups of data	Mean ± SD or frequency (%)	Median (range)
Age (years)	245	58.24±16.47	59.00 (19, 92)
Sex, n	245		
Male		137 (55.9)	
Female		108 (44.1)	
Malignancy, n	245	39 (15.9)	-
Liver cirrhosis, n	245	31 (12.7)	-
Pancreatitis, n	245	14 (5.7)	-
Thrombus, n	245	46 (18.8)	-
Bleeding, n	245	39 (15.9)	-
Biliary infection, n	245	3 (1.2)	-
D-dimer (mg/L) (reference range: 0.01–0.55 mg/L)	245	1.74±4.61	0.42 (0.10, 45.81)
Fibrinogen (g/L) (reference range: 2.00-4.00 g/L)	245	3.52±1.38	3.26 (0.69, 9.13)
WBC (10 ⁹ /L) (reference range: 3.5×10 ⁹ –9.5×10 ⁹ /L)	243	6.38±2.35	6.00 (1.4, 16.5)
GR% (%) (reference range: 40–75%)	243	62.68±11.36	61.70 (35.6, 92.5)
NE (10 ⁹ /L) (reference range: 1.8×10 ⁹ –6.3×10 ⁹ /L)	243	4.14±2.14	3.60 (0.6, 13.3)
LY% (%) (reference range: 20-50%)	243	27.35±10.49	28.00 (4.6, 54.0)
LY (10 ⁹ /L) (reference range: 1.1×10 ⁹ –3.2×10 ⁹ /L)	243	1.63±0.63	1.60 (0.3, 3.5)
RBC (10 ¹² /L) (reference range: female, 3.8×10 ¹² –5.1×10 ¹² /L; male, 4.3×10 ¹² –5.8×10 ¹² /L)	243	4.09±0.83	4.19 (1.32, 5.86)
HB (g/L) (reference range: female, 115-150 g/L; male, 130-175 g/L)	243	120.98±26.63	126.00 (44, 179)
Hematocrit (%) (reference range: female, 35-45%; male, 40-50%)	243	36.77±8.63	38.00 (13.2, 93.2)
PLT (10 ⁹ /L) (reference range: 125×10 ⁹ –350×10 ⁹ /L)	243	213.13±87.94	205.00 (23, 831)
MPV (fL) (reference range: 6–11.5 fL)	243	8.25±1.04	8.10 (6.1, 12.1)
Platelet hematocrit (%) (reference range: female, 0.114-0.287%; male, 0.108-0.272%)	243	0.17±0.06	0.17 (0.02, 0.53)
CRP (mg/L) (reference range: ≤10 mg/L)	67	27.53±61.89	7.10 (0.50, 397.60)
hsCRP (mg/L) (reference range: 0–3 mg/L)	183	14.37±32.54	2.10 (0.1, 206.3)
PCT (ng/mL) (reference range: 0–0.05 ng/mL)	19	0.37±0.49	0.22 (0.03, 1.97)
Blood culture detection, n	245	5 (2.0)	-
Positive bacteria on the blood culture, n	5	3 (60.0)	-

WBC, white blood cell; GR%, percentage of neutrophils; NE, neutrophil count; LY%, lymphocyte percentage; LY, lymphocyte count; RBC, red blood cell; HB, hemoglobin; PLT, platelet count; MPV, mean platelet volume; CRP, C reaction protein; hsCRP, high sensitive C reaction protein; PCT, procalcitonin.

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Table 2 Correlation analysis of D-dimer in all patients

Variables	No. groups of data	Pearson coefficient	P value	Spearman coefficient	P value
Age (years)	245	0.235	<0.001	0.478	<0.001
Sex	245	0.189	0.003	0.090	0.162
Malignancy, n	245	0.272	<0.001	0.312	< 0.001
Liver cirrhosis, n	245	0.178	0.005	0.367	< 0.001
Pancreatitis, n	245	-0.040	0.533	0.079	0.216
Thrombus, n	245	0.215	0.001	0.452	< 0.001
Bleeding, n	245	0.106	0.098	0.122	0.058
Biliary infection, n	245	0.340	<0.001	0.183	0.004
Fibrinogen (g/L)	245	0.118	0.065	0.199	0.002
WBC (10 ⁹ /L)	243	0.176	0.006	0.076	0.239
GR% (%)	243	0.221	0.001	0.360	<0.001
NE (10 ⁹ /L)	243	0.211	0.001	0.172	0.007
LY% (%)	243	-0.237	<0.001	-0.410	<0.001
LY (10 ⁹ /L)	243	-0.164	0.010	-0.388	<0.001
RBC (10 ¹² /L)	243	-0.227	<0.001	-0.398	<0.001
HB (g/L)	243	-0.202	0.002	-0.413	<0.001
Hematocrit (%)	243	-0.190	0.003	-0.393	<0.001
PLT (10 ⁹ /L)	243	-0.130	0.043	-0.195	0.002
MPV (fL)	243	0.015	0.815	0.082	0.200
Platelet hematocrit (%)	243	-0.170	0.008	-0.234	<0.001
CRP (mg/L)	67	0.264	0.031	0.640	<0.001
hsCRP (mg/L)	183	0.368	<0.001	0.610	<0.001
PCT (ng/mL)	19	0.320	0.182	0.693	0.001
Blood culture detection	245	0.071	0.270	0.148	0.021
Positive bacteria on the blood culture	5	0.074	0.906	<0.001	1.000

WBC, white blood cell; GR%, percentage of neutrophils; NE, neutrophil count; LY%, lymphocyte percentage; LY, lymphocyte count; RBC, red blood cell; HB, hemoglobin; PLT, platelet count; MPV, mean platelet volume; CRP, C reaction protein; hsCRP, high sensitive C reaction protein; PCT, procalcitonin.

tests demonstrated that D-dimer positively correlated with age, sex, malignancy, liver cirrhosis, thrombus, biliary infection, WBC, GR%, NE, CRP, and hsCRP, but negatively correlated with LY%, LY, RBC, HB, hematocrit, PLT, and platelet hematocrit. Spearman non-parametric tests demonstrated that D-dimer positively correlated with age, malignancy, liver cirrhosis, thrombus, biliary infection, FIB, GR%, NE, CRP, hsCRP, PCT, and blood culture

detection, but negatively correlated with LY%, LY, RBC, HB, hematocrit, PLT, and platelet hematocrit.

Correlation of D-dimer with clinical and laboratory data in patients with pancreatitis was shown in *Table 3*. Pearson chi-square tests demonstrated that D-dimer positively correlated with PCT, but negatively correlated with LY, RBC, HB, and hematocrit. Spearman non-parametric tests demonstrated that D-dimer positively correlated with

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Table 3 Correlation analysis of D-dimer in patients with pancreatitis

Variables	No. groups of data	Pearson coefficient	P value	Spearman coefficient	P value
Age (years)	14	0.508	0.064	0.300	0.298
Sex	14	0.390	0.168	0.378	0.182
Fibrinogen (g/L)	14	0.240	0.408	0.512	0.061
WBC (10 ⁹ /L)	14	-0.236	0.418	0.009	0.976
GR% (%)	14	0.327	0.253	0.350	0.220
NE (10 ⁹ /L)	14	-0.139	0.636	0.182	0.533
LY% (%)	14	-0.390	0.168	-0.305	0.288
LY (10 ⁹ /L)	14	-0.559	0.038	-0.502	0.067
RBC (10 ¹² /L)	14	-0.830	<0.001	-0.686	0.007
HB (g/L)	14	-0.839	<0.001	-0.695	0.006
Hematocrit (%)	14	-0.810	<0.001	-0.675	0.008
PLT (10 ⁹ /L)	14	-0.023	0.938	0.379	0.182
MPV (fL)	14	0.227	0.435	0.130	0.658
Platelet hematocrit (%)	14	0.105	0.720	0.246	0.396
CRP (mg/L)	8	-0.030	0.944	0.690	0.058
hsCRP (mg/L)	9	0.254	0.509	0.750	0.020
PCT (ng/mL)	7	0.926	0.003	0.893	0.007

WBC, white blood cell; GR%, percentage of neutrophils; NE, neutrophil count; LY%, lymphocyte percentage; LY, lymphocyte count; RBC, red blood cell; HB, hemoglobin; PLT, platelet count; MPV, mean platelet volume; CRP, C reaction protein; hsCRP, high sensitive C reaction protein; PCT, procalcitonin.

hsCRP, and PCT, but negatively correlated with RBC, HB, and hematocrit.

Correlation of D-dimer with clinical and laboratory data in patients with liver cirrhosis was shown in *Table 4*. Pearson chi-square tests demonstrated that D-dimer positively correlated with age, and hsCRP. Spearman non-parametric tests demonstrated that D-dimer positively correlated with age, WBC, and MPV, but negatively correlated with FIB.

Discussion

D-dimer test becomes more and more popular in clinical practice, because it is cheap and readily available. The value of D-dimer in digestive diseases has been also reported. Our study aimed to explore whether D-dimer reflected the inflammation conditions in unselected patients with digestive diseases. We found that D-dimer level was significantly associated with WBC, GR%, and NE, which are the classical

inflammation parameters. We also found a significantly positive correlation of D-dimer level with several novel inflammatory parameters, such as CRP, hsCRP, and PCT.

CRP is an acute phase reaction protein synthesized by the liver, which is associated with inflammation (12). The concentration of CRP positively correlated with the severity of acute pancreatitis (13). Gupta *et al.* included 110 patients with acute pancreatitis and 50 healthy controls and compared the biochemical and hemostatic parameters between the groups on the first and third day (14). They found that the level of D-dimer had a positive correlation with CRP in patients with acute pancreatitis, and a combination of D-dimer and CRP can predict the severity of acute pancreatitis more accurately. By comparison, in the subgroup analysis of patients with pancreatitis, we did not find any significant correlation between the two laboratory parameters. The causes for this unexpected finding should be as follows: (I) only nine patients were diagnosed with

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Table 4 Correlation analysis of D-dimer in patients with liver cirrhosis

Variables	No. groups of data	Pearson coefficient	P value	Spearman coefficient	P value
Age (years)	31	0.584	0.001	0.379	0.035
Sex	31	0.180	0.332	-0.073	0.696
Fibrinogen (g/L)	31	-0.194	0.295	-0.391	0.030
WBC (10 ⁹ /L)	29	0.191	0.320	0.393	0.035
GR% (%)	29	0.018	0.925	0.167	0.387
NE (10 ⁹ /L)	29	0.083	0.667	0.259	0.176
LY% (%)	29	0.011	0.957	-0.139	0.471
LY (10 ⁹ /L)	29	0.173	0.370	0.235	0.220
RBC (10 ¹² /L)	29	-0.024	0.903	-0.335	0.076
HB (g/L)	29	0.130	0.500	-0.166	0.391
Hematocrit (%)	29	0.115	0.552	-0.187	0.331
PLT (10 ⁹ /L)	29	-0.150	0.438	-0.050	0.799
MPV (fL)	29	0.206	0.285	0.399	0.032
Platelet hematocrit (%)	29	-0.103	0.597	0.017	0.930
CRP (mg/L)	4	0.491	0.509	-0.200	0.800
hsCRP (mg/L)	11	0.729	0.011	0.409	0.212
Blood culture detection	31	-0.026	0.888	-0.059	0.754
Positive bacteria on the blood culture	2	NA	NA	NA	NA

WBC, white blood cell; GR%, percentage of neutrophils; NE, neutrophil count; LY%, lymphocyte percentage; LY, lymphocyte count; RBC, red blood cell; HB, hemoglobin; PLT, platelet count, MPV: mean platelet volume; CRP, C reaction protein; hsCRP, high sensitive C reaction protein; PCT, procalcitonin; NA, not available.

pancreatitis in our study; and (II) there were only eight groups of data with both D-dimer and CRP.

PCT and hsCRP are employed for the diagnosis and differential diagnosis of bacterial infection (15). PCT with a cut-off value of 0.5 ng/mL is a biomarker for bacterial infections in patients with liver cirrhosis at the emergency department (16). Lin *et al.* explored the PCT and CRP levels for bacterial infection in 1,144 patients with liver cirrhosis (17). Among them, 435 patients had bacterial infection episodes (32.1%). The pooled sensitivity estimates were 79% for PCT tests and 77% for CRP tests. The pooled specificity estimates were 89% for PCT tests and 85% for CRP tests. Both PCT and CRP tests have acceptable accuracy for diagnosing bacterial infection among patients with liver cirrhosis. Wu *et al.* explored the prediction of the PCT and CRP levels for spontaneous bacterial peritonitis (SBP) in 88 patients with advanced

cirrhosis (18). Among them, 40 patients were diagnosed with SBP and 48 patients with culture-negative neutrocytic ascites. The CRP and PCT before antibiotics treatment were detected. They found that the serum PCT levels were significantly higher in advanced liver cirrhotic patients with SBP than in those with culture-negative neutrocytic ascites. The serum level of PCT can improve the accuracy of early diagnosis of SBP in advanced liver cirrhosis. Kadam et al. evaluated the prognostic role of hsCRP for SBP in 100 patients with liver cirrhosis (19). Among them, 50 patients had acute bacterial peritonitis as a study group and 50 patients had sterile ascites as a control group. The hsCRP level was compared between them. The hsCRP level was evaluated 5 days after antibiotic therapy for SBP. The mean hsCRP level was significantly higher in the patients with SBP before antibiotic therapy than in those without SBP (P=0.0001). The mean hsCRP level was significantly AME Medical Journal, 2017 Page 7 of 8

lower at the 5th day or discharge after antibiotic therapy than before antibiotic therapy (P<0.05). Thus, the hsCRP level should be a surrogate marker of SBP in liver cirrhosis. Unfortunately, in the subgroup analysis of liver cirrhosis, no patient underwent D-dimer or PCT detection. Thus, we could not evaluate this issue in this subgroup.

Dias *et al.* explored the predictive ability of PCT strip test for acute pancreatitis in 50 patients (20). They found that the sensitivity and specificity of PCT with a cut-off value of >2 ng/mL were all 100% for predicting the progression to severe acute pancreatitis, and that the sensitivity and specificity of PCT with a cut-off value of >0.5 ng/mL were 100% and 80% for predicting antibiotic requirement, respectively. Plasma PCT is an early and reliable prognostic indicator in acute pancreatitis. The PCT strip test is a rapid and useful test for analyzing the prognosis of patients with acute pancreatitis. Our study found a very close correlation between D-dimer and PCT in patients with pancreatitis, but only seven groups of data were included.

We are used to conducting a blood culture detection and antimicrobial susceptibility in the cases of fever with a temperature of >38.5 °C and making a diagnosis of bacteremia based on the blood culture detection. Our study showed that D-dimer had a positive correlation with blood culture detection, which provided indirect evidence regarding the association of D-dimer with inflammation.

Our study had several limitations. First, the number of patients enrolled in this study was relatively small and the enrollment period was short. Second, all patients were treated by the same physician, and there was a patient selection bias. Third, there was a small number of patients with critical illness. Fourth, we did not focus on a specific digestive disease as the study population. Fifth, not all patients underwent the detection of inflammatory markers at the same time of D-dimer tests.

In conclusion, D-dimer may reflect an inflammatory condition in unselected patients with digestive diseases. In the cases of higher D-dimer, we should not neglect the possibility of inflammation. Further validation study should focus on the patients with specific digestive diseases.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The study protocol was approved by the Medical Ethical Committee of our hospital. The ethical approval number is k (2016) 37. The patient written informed consent was not required.

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