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Diagnostic and Prognostic Value of Plasma Factor V Activity and Parameters in Thrombin Generation for Disseminated Intravascular Coagulation in Patients with Hematological Malignancies

Hai-ming KOU[1, 2†], Xiao-ping ZHANG[1, 2†], Man-zhi WANG[1, 2], Jun DENG[1, 2], Heng MEI[1, 2], Yu HU[1, 2#]
[1]*Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China*
[2]*Hubei Clinical and Research Center of Thrombosis and Hemostasis, Wuhan 430022, China*

Summary: In this study, we used plasma factor V activity and parameters of the thrombin generation test to discuss their diagnostic and prognostic value for disseminated intravascular coagulation (DIC) in patients with hematological malignancies. A total of 164 patients who were diagnosed with hematological malignancies in the Department of Hematology, Union Hospital, between Apr. 2014 and Dec. 2014 were enrolled in this study. There were 131 patients in the study group and 33 patients in the control group in terms of the laboratory results for DIC. The patients in the study group were divided into a DIC subgroup (n=59) and a non-DIC subgroup (n=72) based on the International Society of Thrombosis and Hemostasis (ISTH) Integral System, and they were divided into four subgroups [score ≤3 (n=35), score=4 (n=37), score=5 (n=47), and score ≥6 (n=12)] according to ISTH scores. Using 28-day mortality as the endpoint, the patients in the study group were divided into a survival subgroup (n=111) and a non-survival subgroup (n=20). The results showed that the plasma factor V activity was significantly weaker, and lag time and time to peak were significantly shorter in the study group than in the control group (P<0.01). The factor V activity, peak and endogenous thrombin potential (ETP) were significantly decreased in the DIC subgroup as compared with those in the non-DIC subgroup (P<0.01). Among factor V activity, lag time, peak, ETP, and ttPeak, only the factor V activity was significantly decreased in the non-survival subgroup compared with the survival subgroup (P<0.01). With the increase in ISTH score, the ETP and peak decreased gradually. The binary logistic regression analysis revealed that PLT, D-dimer, factor V activity and ETP had linear relationship with DIC diagnosed by ISTH Integral System. Using DIC diagnosed by ISTH Integral System as the endpoint, the area under curve (AUC) of factor V activity was found to be similar to that of blood platelet count (PLT) and prothrombin time (PT). In conclusion, factor V activity, ETP and peak had diagnostic value for DIC in patients with hematological malignancies, and only factor V activity had limited prognostic value.
Key words: disseminated intravascular coagulation; hematological malignancies; factor V activity; thrombin generation test

Disseminated intravascular coagulation (DIC) is an acquired syndrome rather than a disease. It is always secondary to an underlying disorder that causes the activation of coagulation[1]. The development of DIC often involves multiple systems such as the coagulation system, anticoagulation system and fibrinolytic system[2]. The clinical manifestations of DIC include bleeding, microcirculatory disorder, microvascular thrombosis and microangiopathic hemolysis. Therefore, DIC is complicated and no single clinical or laboratory test has an adequate sensitivity and specificity to confirm or reject a diagnosis of DIC[3].

Currently, most scholars have proposed and accepted use of integrating systems to diagnose DIC, including the International Society of Thrombosis and Hemostasis standard (ISTH)[4], the Japanese Health and Welfare Ministry standards (JMHW)[5] and the Japanese Society of Emergency Medicine standards (JAAM)[6]. There are many prospective studies on the integrating systems[7–9], but it is still a challenge to accurately diagnose DIC with abundant professional experience needed.

The relationship between DIC and factor V activity has rarely been referred to. To our knowledge, the change in factor V activity in patients with hematologic malignancies has not been reported yet, and the correlation between DIC and parameters of the

Hai-ming KOU, E-mail: yzgumu@126.com; Xiao-ping ZHANG, E-mail: 28975426@qq.com
†These authors contributed equally to this work.
#Corresponding author, E-mail: dr_huyu@126.com

thrombin generation test in hematologic malignancies has not been fully explored. The present study aimed to find out the diagnostic and prognostic value of plasma factor V activity and parameters in thrombin generation for DIC in patients with hematological malignancies.

1 MATERIALS AND METHODS

1.1 Laboratory Methods and Specimen Processing

A total of 164 patients were enrolled in this study and they were diagnosed with hematological malignancies during hospitalization from Apr. 2014 to Dec. 2014 at the Department of Hematology, Union Hospital, Wuhan, China. There were 164 plasma specimens in this study, including 131 patients in the study group and 33 patients in the control group. In the study group, the ratio of male:female was 77:54, and the average age was 43.93±16.37 years. In the control group, the ratio of male:female was 18:15, and the average age was 42.48±14.38 years. Patients enrolled in this study were diagnosed with acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), chronic leukemia (CL), multiple myeloma (MM), lymphoma or myelodysplastic syndromes (MDS) associated with leukemia. The laboratory results of patients should meet at least one of the following requirements[1, 2]: fibrinogen degradation products (FDP) >10 μg/mL; fibrinogen (Fbg) <1 g/L; prolongation of prothrombin time (PT) >3 s. Exclusion criteria[1–6] were as follows: age <15 years; using anticoagulant drugs before enrollment; liver cirrhosis classified as Child-Pugh grade C; known coagulopathy; thrombotic thrombocytopenic purpura (TTP); antiphospholipid syndrome (APS, diagnosed according to the Sapporo criteria[10]) etc. The patients in the control group had no obvious abnormal results representing DIC. We collected the information from clinical medical records of the patients. There were no statistically significant differences in gender and age between the study group and the control group (P>0.05).

Specimens were stored at –80°C until analysis. The factor V activity was measured by the STAGO Automatic Coagulation Analyzer (solidification method, French). The coagulation method was used to determine activated partial thromboplastin time (APTT), PT, Fbg, FDP, antithrombin activity (ATA). Using immunoturbidimetry, D-dimer was tested. The thermo scientific detector (Thermo Fisher Scientific, USA) was used to detect the parameters of thrombin generation test by automatic correction of thrombin curve method. The DIC state was evaluated by the ISTH integral system[4].

1.2 Evaluation of Specimens by DIC Diagnosis Criteria Based on ISTH Integral System in Study Group

In the study group, 59 patients who met the standard of ISTH fell into the DIC subgroup, and the rest of 72 patients served as non-DIC subgroup. At the same time, the study group was divided into four subgroups [score ≤3 (n=35), score=4 (n=37), score=5 (n=47), and score ≥6 (n=12)] according to ISTH scores.

1.3 Subgrouping of Study Group by 28-day Mortality as Endpoint

Using 28-day mortality as the endpoint, the study group was divided into a survival subgroup and a non-survival subgroup. A total of 111 patients were in the survival subgroup, and 20 in the non-survival subgroup.

1.4 Statistical Method

SPSS18.0 statistical software was used for data analysis. Measurement data were expressed as the mean±standard deviation (SD) and the difference between the continuous data was compared with the t-tests. The difference between categorical variables was compared with chi square tests. The binary linear regression analysis was made to evaluate the influence of factor V activity, laboratory indexes for DIC, age and sex on DIC diagnosed by ISTH Integral System. Through the Med-Calc software, we analyzed the receiver operating characteristic curve (ROC curve) of DIC diagnosed by ISTH Integral System to determine the diagnostic efficacy of each parameter in the study group. A P value less than 0.05 was considered statistically significant.

2 RESULTS

2.1 Comparison of Each Parameter of the Thrombin Generation Test and Factor V Activity between Different Groups and Subgroups

The plasma factor V activity and parameters of thrombin generation test were used to discuss their diagnostic and prognostic value for DIC in hematological malignancies. First, we selected the mean±SD to understand the difference between different groups and subgroups. The factor V activity in the study group (69.65%±32.96%) was significantly decreased as compared with that in the control group (100.06%±16.47%) (P<0.05). The same situation happened between the DIC subgroup and the non-DIC subgroup or between the survival subgroup and the non-survival subgroup (P<0.05). The thrombin generation test involved four parameters: lag time, time to peak (ttPeak), peak and endogenous thrombin potential (ETP). Among these parameters, the lag time (3.67±1.61 min) and ttPeak (6.48±2.09 min) in the study group were significantly prolonged (P<0.05) when compared with those in the control group (2.38±0.45 min and 5.48±1.51 min, respectively). However, there was no statistically significant difference in ETP (951.71±447.24 *vs.* 933.99 ±162.65 nmol/L) and peak (166.90±74.44 *vs.* 174.74±45.13 nmol/L) between the study group and the control group. The peak and

ETP were significantly different (P<0.05) between the DIC subgroup and the control group, but there was no significant difference in the peak and ETP between the non-DIC subgroup and the control group. Between the DIC subgroup and the non-DIC subgroup, the differences in lag time and ttPeak were not statistically significant, but those in ETP and peak were statistically significant (P<0.05). Between the survival subgroup and the non-survival subgroup, the differences in lag time, peak, ETP and ttPeak were not statistically significant (table 1).

2.2 Comparison of Each Parameter of the Thrombin Generation Test and Factor V Activity among Different ISTH Scores Subgroups

To discuss whether parameters of the thrombin generation test and factor V activity are correlated with the severity of DIC, we divided the study group into four subgroups [score ≤3 (n=35), score=4 (n=37), score=5 (n=47), and score ≥6 (n=12)] according to ISTH scores. As shown in fig. 1, it was found that from score=4, with the increases in the ISTH scores, factor V activity decreased significantly, and there existed a statistically significant difference (P<0.05). From score=4, with the increases in the ISTH scores, the lag time and ttPeak decreased gradually, but no statistically significant difference existed between the adjacent subgroups. From score ≤3, with the increases in the ISTH scores, the ETP and peak decreased gradually, and there were statistically significant differences between the subgroups of score=4 and score=5 and between the subgroups of score=5 and score ≥6 (fig. 1).

2.3 ROC Curve Analysis

In the study group, using DIC diagnosed by ISTH Integral System as the endpoint, the area under the curves (AUC) of factor V activity, D-dimer, Fbg, FDP, PLT, PT, lag time, ETP, peak and ttPeak were found to be 0.682, 0.912, 0.764, 0.935, 0.694, 0.692, 0.611, 0.775, 0.719 and 0.612, respectively (fig. 2).

2.4 Logistic Regression Analysis

We included age, gender, APTT, PT, fibrinogen, FDP and D-dimer, PLT, factor V activity, lag time, ETP, peak, ttPeak into the logistic regression analysis of the DIC diagnosis by ISTH criteria. The binary logistic regression analysis showed that items whose P values were less than 0.05 were D-dimer (0.003), PLT (0.004), factor V activity (0.032), and ETP (0.013).

3 DISCUSSION

Although the diagnosis and treatment of DIC are continuously improved, it is still a very severe clinical syndrome. Early diagnosis may effectively reduce the mortality of DIC patients[11]. Recently, more and more molecular markers have been explored for the diagnosis of DIC, but mainly for DIC with sepsis. DIC is a wasting disease, and in the process of the development of DIC, the body consumes a large amount of blood coagulation factor[12]. Factor V is a very important coagulation factor in the coagulation process, and its change in the process of DIC remains unknown. In the present study, it was found that the plasma factor V activity decreased significantly in the study group (*vs.* control group),

Table 1 Comparison of each parameter of the thrombin generation test and factor V activity between diffent subgroups

Variables	DIC subgroup (n=59)	Non-DIC subgroup (n=72)	Survival subgroup (n=111)	Non-survival subgroup (n=20)
Clinical diagnoses				
AML-M3	16	10	24	2
AML except AML-M3	23	29	38	14
ALL	10	10	18	2
CL	1	10	10	1
Lymphoma	7	5	12	0
Other diseases	2	8	9	1
Factor V activity (%)	55.22±28.29	78.43±32.63	69.32±32.65	47.70±26.61
Lag time (min)	3.56±1.95	3.81±1.33	3.73±1.68	3.52±1.36
ETP (nmol/L)	706.61±313.02	1090.58±478.69	941.74±469.80	783.92±327.08
Peak (nmol/L)	132.64±59.58	184.10±68.60	163.59±72.44	146.11±47.88
Time to peak (min)	6.24±2.58	6.68±1.71	6.58±2.17	5.93±1.98
PLT ($\times 10^9$)	29.92±18.42	83.86±150.67	64.57±124.17	31.8±24.91
PT (s)	17.86±3.44	15.78±2.08	16.35±2.70	18.75±3.53
APTT (s)	45.97±10.08	44.57±8.88	44.15±9.10	51.01±9.33
FDP (μg/mL)	72.37±37.86	19.29±22.28	41.17±39.78	54.48±41.45
D-dimer (μg/mL)	14.68±.5.97	4.92±4.39	8.88±7.00	11.72±7.28
Fbg (mg/dL)	2.24±1.37	3.76±1.81	3.14±1.75	2.71±1.97
ATA (%)	82.83±21.64	78.85±24.65	82.40±23.06	70.90±23.01

DIC: disseminated intravascular coagulation; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CL: chronic leukemia; MM: multiple myeloma; MDS: myelodysplastic syndrome; ETP: endogenous thrombin potential; ROC: receiver operating characteristic; PT: prothrombin time; APTT: activated partial thromboplastin time; FDP: fibrin/fibrinogen degradation products; ATA: antithrombin activity

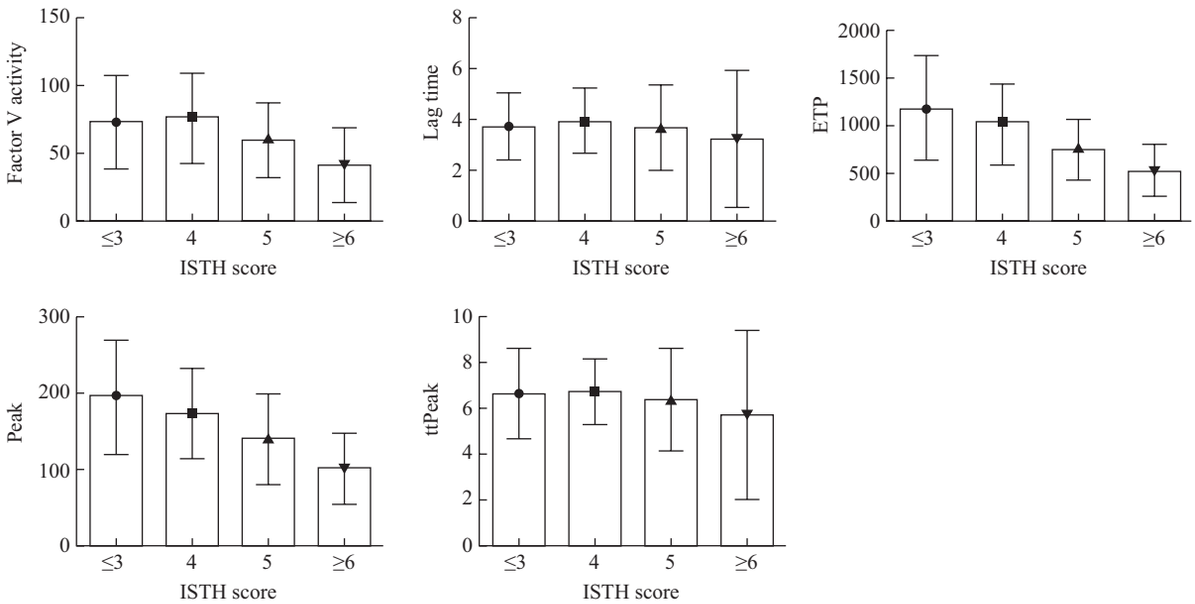

Fig. 1 Correlation between different parameters and ISTH scores

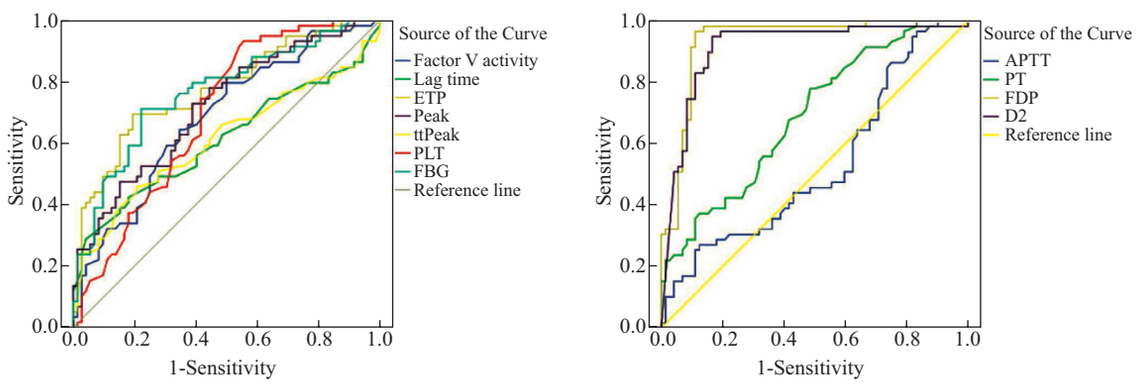

Fig. 2 Evaluation of the diagnostic efficacy of each parameter by using ROC curve analysis
ETP: endogenous thrombin potential; Fbg: fibrinogen; FDP: fibrin/fibrinogen degradation products; PLT: platelet; PT: prothrombin time

DIC subgroup (*vs.* non-DIC subgroup) and survival subgroup (*vs.* non-survivor subgroup). ISTH scoring system is a widely used diagnostic criteria for DIC, and the score of ISTH reflects the severity of DIC in some ways. We divided the study group into different subgroups according to the score of ISTH. It was found that from score=4, with the increases in the ISTH scores, the factor V activity decreased significantly, and there existed a statistically significant difference between different score subgroups (P<0.05). Most patients with DIC showed a decrease in plasma factor V activity that was associated with the severity of DIC. However, not all patients had a significant reduction of factor V activity. We speculate that in some patients, the factor V activity was very high before DIC, and DIC that occurred accidentally was not able to decrease factor V activity below normal level soon enough. In consideration of this, a progressive decrease of factor V activity, we believe, can illustrate the problem better. In the new DIC integral scoring system of the Japanese Association for Acute Medicine[5], similar to platelet decline as an important supplement, a decline in factor V activity can also act as an important supplement to evaluate DIC. This is because DIC consumes not only platelets but also factor V. Nevertheless, whether there is a change of synchronization between them is unknown. In future researches, we will attempt to harvest more specimens and more data from patients at different periods to verify this hypothesis.

In patients with liver disease, with the blood coagulation factor reduced, research showed that the value of factor V activity in the judgment of risk of patients to develop fulminant hepatic failure is very high[13]. But for patients with DIC, the prognostic value of factor V activity has been barely mentioned. In our study, there was a significant difference in factor V

activity between the survival subgroup and the non-survival subgroup, indicating that the factor V activity holds promises to predict the prognosis of DIC patients.

The analysis of the ROC curve, using DIC diagnosed by ISTH Integral System as the endpoint, showed that the value of AUC associated with factor V activity was similar to those of PLT and PT, and PLT and PT were important integral items in ISTH integral system, which played an important role in the diagnosis of DIC. In logistics regression analysis, the factor V activity was also found to be correlated with the diagnosis of DIC.

As for the parameters of thrombin generation test, the lag time and ttPeak were significantly decreased in the study group compared to the control group, but no significant difference was noted in the lag time and ttPeak between the DIC subgroup and the non-DIC subgroup. The peak and ETP in the DIC subgroup were significantly different from those in the non-DIC subgroup, and there was no significant difference in the peak and ETP between non-DIC subgroup and control group. This indicated that a large amount of thrombin was consumed in the acute phase of DIC, the thrombin generation capacity was insufficient, and the peak and ETP showed significant diagnostic value for DIC. Using DIC diagnosed by ISTH Integral System to evaluate the outcome of each parameter in the binary logistic regression analysis, only ETP was shown to have significant correlation with DIC. The ROC curve analysis showed that the value of AUC associated with peak and ETP was similar to that of Fbg. Fbg was an important integral item in ISTH Integral System, too. Some study also showed that ETP has a high value in the evaluation of the prognosis of DIC by using 120-day mortality as the standard[14].

In conclusion, our study demonstrated that the decreased plasma activity of factor V was tightly related to the severity and mortality of DIC in patients with hematological malignancies. In addition, the measurement for factor V activity is simple and stable. Plasma factor V activity may be used as a molecular marker for the diagnosis and prognostic evaluation of DIC in patients with hematological malignancies. As for ETP and peak, although their results were tightly related to the severity of DIC in patients with hematological malignancies, they may have limited diagnostic value because of the limitations of testing.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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