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Original Article

Can very high level of D-dimer exclusively predict the presence of thromboembolic diseases?

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Abstract

Background: D-dimer quantitative test is mainly used to rule out the presence of thromboembolic diseases (TEDs). Whether very high D-dimer (100 times above the cutoff point) can exclusively indicate the presence of TED should be known.

Methods: D-dimer was detected by a quantitative immunoturbidimetric assay. The normal value is 0.2−0.7 mg/L fibrinogen equivalent units (FEUs). During the year of 2009, 1,053 D-dimer tests were performed. We analyzed the results of these patients to find out the causes of very high D-dimer.

Results: The mean value of D-dimer in the 1,053 tests was 8.56 mg/L FEU, ranging from <0.2 mg/L to 563.2 mg/L FEU. Of them, 28 samples from 21 patients had very high D-dimer value: >50 mg/L FEU. Of the 21 patients, 9 (43%) had TED, 1 had suspected TED, but not proved by computed tomographic (CT) angiogram, 3 had massive gastrointestinal or other site bleeding, 3 patients had cardiac arrest with samples taken immediately after recovery from cardiopulmonary resuscitation (CPR), 2 had sepsis with disseminated intravascular coagulation (DIC), 1 had postpartum hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome with acute pulmonary edema and renal failure, 1 had multiple traumatic injury, and 1 received thrombolytic therapy.

Conclusion: Although TED was the most frequently seen disorder in patients with very high D-dimer value, very high D-dimer was not necessary exclusively the marker of TED. Other disorders such as massive bleeding, status post CPR, sepsis with DIC, multiple traumatic injuries, hyperfibrinolysis and HELLP syndrome can also have very high D-dimer.

Keywords: D-dimer; Diagnosis; Thromboembolic diseases

1. Introduction

Thromboembolic diseases (TEDs) remain a major cause of morbidity and mortality in many countries. Early recognition and appropriate treatment are required to save life and reduce complications. Thanks to the advancement of new diagnostic tools, more TED can be diagnosed by non-invasive methods, i.e. Doppler ultrasound, helical computed tomographic (CT) angiography, lung perfusion/ventilation scan and magnetic resonance angiography (MRA). However, some TED cannot be easily diagnosed by these methods; for example, small-vessel pulmonary embolism is not easily shown by most of the non-invasive imaging methods. While the abovementioned methods are aimed to positively diagnose the presence of TED, D-dimer test is usually designed to exclude the presence of TED.[1−5] If D-dimer value is lower than the cutoff point, we can exclude the presence of TED, and the negative predictive value of a negative D-dimer test in a low-risk patient can be very high, even close to 100%, depending on the sensitivity of the assays and the selected populations.[6−9] Therefore, in some uncertain cases, if we get a low D-dimer value, we can affirm the absence of TED. Thus, the main aim of measuring D-dimer is to rule out the presence of TED, but not rule in the presence of TED.

Recently, a few studies tried to know if high D-dimer level could have positive predictive values of TED. Bosson et al.[10] reported that high D-dimer value was predictive of the

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occurrence of pulmonary embolism in a selected population with low-risk factor. Lindahl et al.[11] suggested that when the threshold value of D-dimer is 4 mg/L, the positive predictive value of TED is high. Kucher et al. and Righini et al. also reported the positive predictive value of TED with a high D-dimer;[12,13] Tick et al. suggested markedly elevated D-dimer levels might increase the likelihood of pulmonary embolism.[14] However, in addition to TED, many other situations, such as bleeding, pregnancy, trauma, post-surgery, atherosclerosis, old age, cancer and inflammatory diseases can cause a high D-dimer,[15] especially in hospitalized patients, and the previous studies didn't show whether very high value of D-dimer could exclusively prove the presence of TED. In the present study, we collected all the D-dimer results of the patients admitted to our hospital in the whole year of 2009. Then we found out the patients with very high level of D-dimer, and analyzed the causes in order to know if very high D-dimer could exclusively prove the presence of TED.

2. Methods

After obtaining consent from the hospital director, we collected all the D-dimer data of our inpatients during the whole year of 2009, from January 1 to December 31 through the Hospital Information Department. We performed the present retrospective study according to the guidelines of our College Ethics Committee. Totally, 1,053 D-dimer tests were measured in the hematology laboratory of our hospital. All the 1,053 D-dimer tests were performed by the commercial kit Innovance* D-Dimer (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). It is a particle-enhanced, immunoturbidimetric assay for the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma for use on coagulation analyzers. All the tests were performed following the manufacturer's instructions. The normal value is 0.2–0.7 mg/L fibrinogen equivalent units (FEUs). The cutoff point to rule out TED was set at 0.5 mg/L FEU or less. Very high D-dimer level was defined as 100 times above the cutoff point, i.e. equal to or greater than 50 mg/L FEU. We analyzed the results of the 1,053 samples, reviewed the history of the patients with very high D-dimer through the hospital computer system, and found out the causes producing very high D-dimer.

3. Results

The mean value of D-dimer in the 1,053 tests was 8.56 (SD 30.87) mg/L FEU, ranging from <0.2 mg/L to 563.2 mg/L FEU, and the median was 2.1 mg/L FEU. Two hundred and sixty-nine tests (25.5%) showed normal value (≤0.7 mg/L FEU), 28 samples (2.7% of total tests) showed very high D-dimer value (>50 mg/L FEU), ranging from 51.0 mg/L to 563.2 mg/L FEU. These 28 samples came from 21 patients. We collected the data of these 21 patients to see the underlying diseases which causing the very high D-dimer.

Of the 21 patients, 9 (43%) were proved to have TED by one or more of the following imaging examinations: Doppler ultrasound, high-probability lung scan, and CT angiogram. Among these nine patients, four had deep vein thrombosis, one had cerebral venous thrombosis, one had portal vein thrombosis, one had artery thrombosis with gangrene of the left leg and two had pulmonary embolism. Twelve patients were found to have other causes: one had chronic obstructive pulmonary disease and ischemic heart disease with sudden onset of shortness of breath, but CT angiogram could not show any evidence of thrombosis, and the patient soon expired. Two had massive gastrointestinal (GI) bleeding, and one had a big right neck hematoma extending to the retropharyngeal space with displacement of the airway. Three had cardiac arrest with samples taken immediately after recovery from cardiopulmonary resuscitation (CPR). Two had sepsis with disseminated intravascular coagulation (DIC), which was proved by positive bacterial cultures, deranged coagulation and fragmented red bleed cells in the peripheral blood smears. One had multiple traumatic injury caused by road traffic accident, and multiple operations done for him. One had acute myocardial infarction, with sample taken 7 hours after thrombolytic therapy. And the last had postpartum hemolysis, elevated liver enzymes, low platelets(HELLP) syndrome, acute renal failure and congestive heart failure with pulmonary edema (Tables 1 and 2).

4. Discussion

D-dimer measurement is a common and simple test, usually available in most hematology laboratories. Although it is simple and convenient to perform, its usage is usually set on exclusion rather than inclusion of TED. If we get a low D-dimer value, the chance of exclusion of TED is high.[7] However, if the D-dimer is high, although the presence of TED is increased as well, we cannot definitely diagnose TED solely by that high D-dimer. Recently, some investigators tried to prove high D-dimer had higher positive predictive value of TED, and the incidence of TED did increase in selected populations with high D-dimer.[10–14] Most of the previous studies focused only on a selected group of population, and compared the incidence of TED with various levels of D-dimer to see if higher D-dimer would have higher incidence of TED. Although the answer seemed to be positive, as many other diseases can also produce high D-dimer, whether very

Table 1
Causes of very high D-dimer in 21 patients

	Number of patients
TED, proved	9
Suspicious pulmonary embolism	1
Status after cardiopulmonary resuscitation	3
Extensive bleeding	3
Sepsis and DIC	2
Road traffic accident with multiple injuries, post operation	1
Post thrombolytic therapy for acute myocardial infarction	1
Postpartum HELLP syndrome, pulmonary edema	1

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, low platelets; TED = thromboembolic diseases.

Table 2
Characteristics of the 12 non-TED patients with very high D-dimer

Possible causes of very high D-dimer	Underlying/associated disorders	*n*
Suspicious pulmonary embolism	COPD, IHD	1
After cardiac arrest	DM, ischemic cardiomyopathy	1
	SCD with ACS	1
	Post coronary artery graft, hematoma	1
Massive bleeding	GI bleeding, massive blood transfusion	1
	SCD, ACS, GI bleeding, ARF, MOF	1
	ALL post chemotherapy, big hematoma, fever	1
Sepsis with DIC	Fanconi anemia, peritonitis, pelvic abscess	1
	SCD, ACS	1
HELLP syndrome	Congestive heart failure, ARF, pulmonary edema	1
Multiple traumatic injuries	Road traffic accident, with major operations	1
Thrombolytic therapy	Acute myocardial infarction	1

ACS = acute chest syndrome; ARF = acute renal failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GI = gastrointestinal; HELLP = hemolysis, elevated liver enzymes, low platelets; IHD = ischemic heart disease; MOF = multi-organ failure; SCD = sickle cell disease.

high D-dimer exists only in TED is another interesting issue which deserves our investigation. The present observational study simply analyzed the causes of very high D-dimer in order to know if very high D-dimer exists exclusively in TED.

Although our present study was a retrospective study, it simply showed the causes of very high D-dimer levels in the hospitalized patients. Among our patients, only 25.5% of them had normal D-dimer, which demonstrated that normal D-dimer was less likely obtained in the hospitalized patients than the general populations. Schrecengost et al. also reported that the percentage of normal D-dimer in hospitalized patients was lower than that in outpatients (18.6% *vs*. 48.1%).[16] It indicates again that many other situations, such as infection, inflammation, surgery, trauma, atherosclerosis, cancer, bleeding and pregnancy, can cause high value of D-dimer, especially in the hospitalized patients.[15] In the present study, as most of our patients (>90%) were inpatients, they had more chance to get very high value of D-dimer than the general population, and more chance to have different kinds of diseases which cause very high D-dimer.

We arbitrarily set 100-fold above the cutoff point to define very high D-dimer value, as we thought that if it could exclusively prove the presence of TED, we might further lower down the value to see at which cutoff point D-dimer might positively predict the presence of TED. However, even when we took 100 times of the cutoff point, we could not exclusively predict the presence of TED, which demonstrates that even for very high D-dimer up to 100 times the normal, no positive predictive value by D-dimer is shown, especially in the hospitalized patients.

Many other causes can also produce high D-dimer, such as massive bleeding, status post CPR, sepsis with DIC and status post thrombolytic therapy. The above three causes are more or less correlated with accelerated coagulation and/or hyperfibrinolysis. For example, in a case of massive bleeding, blood clotting will actually occur and secondary fibrinolysis follow. Patients resuscitated from cardiac arrest might have a certain period of blood stasis due to cardiac arrest, and thus might have some degree of thrombosis and secondary activation of the fibrinolytic system, resulting in a very high level of D-dimer. In patients with DIC, simultaneous activations of both the coagulation system and fibrinolytic system are the pathological processes which will result in very high value of D-dimer. As for patients with thrombolytic therapy, high D-dimer level will obviously be obtained due to lysis of the blood clot.

For our patient with multiple traumatic incidence resulted from road traffic accident, blood vessel interruption and endothelial damage might have occurred, which may have disturbed the hemostatic balance to the propensity of thrombosis. Furthermore, multiple operations were done for this patient, which would have further damaged the vessels and the endothelial cells, resulting in accelerated blood clotting, secondary fibrinolysis and thus, very high level of D-dimer.

For the patient with postpartum HELLP syndrome, it was interesting to find a very high D-dimer in her. HELLP syndrome is currently regarded as a variant of severe preeclampsia,[17] with activation of vascular endothelium and platelets, resulting in the development of DIC.[18] Increased coagulation activity such as decreased protein C and antithrombin levels, and increased thrombin-antithromin level were found[19] in these patients. They might also have compensated DIC and thrombotic tendency,[19,20] as well as high D-dimer level.[20,21] Our patient had not only HELLP syndrome, but also developed pulmonary edema and renal failure which were possibly induced by microangiopathy and DIC.[17,22] Thus, due to the above-mentioned hypercoagulation changes in HELLP syndrome, there can be no doubt very high D-dimer was produced.

The main limitation of the present study is that it is a retrospective study, thus, not so many aggressive investigations were done to exclude the coexistence of thrombosis. For example, in the patients with severe GI bleeding, as no other signs of thrombosis such as swelling of the lower legs or shortness of breath occurred; only the essential examinations were done to investigate the cause of bleeding. However, there was no evidence to show the coexistence of thrombosis in such cases by the necessary investigations which were thought to be important for the patients. Thus, for the patients without symptoms or signs of thrombosis, only the most reasonable investigations were done, which might not be enough to rule

out the coexistence of thrombosis. Another limitation is that our patients were inpatients, so the results of the present study might not be applied to the general population, in whom the higher D-dimer value might have highest chance of TED, as most of the other situations occurring in the hospitalized patients will not easily occur in the general population.

Although our study has its limitations, the causes of very high D-dimer were found and all the causes were reasonable enough to explain the high D-dimer. As our data demonstrated that very high level D-dimer is not an exclusive predictor for TED, further prospective study should be conducted to give us more definite conclusion.

In conclusion, although the possibility of TED is high in patients with very high level of D-dimer, it is not an exclusively positive predictor of TED. Other situations which may produce very high D-dimer still exist.

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