Editorial

Re-visiting D-dimers and fibrin degradation products for the diagnosis of acute aortic dissection

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Acute aortic dissection (AAD), the most severe form of acute aortic syndrome, is a catastrophic condition and a challenge to physicians (1). The heterogeneous clinical presentations of AAD may delay a correct diagnosis and proper management, which affects surgical outcomes and long-term consequences (2). The prevalence of AAD in emergency departments was estimated to be 1 in 10,000 from a report in 2012 (3). About 27% AAD patients present with a classical triad of sudden and severe tearing chest pain, an extremity blood pressure differential of >20 mmHg, and a widened mediastinum observed in chest radiographs (3,4). On the other hand, nearly 4% patients with AAD present none of the classical symptoms (4). The presence of non-classical symptoms, thereby a common clinical scenario of AAD, tended to delay diagnosis for longer than 12 hours as compared with the median time of 3 hours (5). A potential for diagnosis delayed for more than 24 hours has been reported in up to 39% patients after hospitalization (4). In addition, over 60% women with AAD are reportedly older than 65 years of age and likely to present atypical symptoms, which leads to delayed diagnosis (1,6). Nonspecific symptoms of the "great masquerader" include angina, abdominal pain, pleural effusion, neurologic symptoms, syncope, dyspnea, and acute limb ischemic pain, and are reported to be commonly present in over 15% patients visiting emergency departments (7). It is of note that acute coronary syndrome was among the most common erroneous diagnoses that led to antithrombotic and antiplatelet therapies (5). These data highlight an unmet medical need in modern medicine for efficient and accurate diagnostic tools to combat AAD.

Imaging studies using computed tomography (CT), magnetic resonance imaging (MRI), or transesophageal echocardiography have shown high sensitivity and specificity (1). However, these imaging tools are invasive and are not the first line screening armamentarium for non-classical AAD symptoms in the emergency departments. Testing for serum biomarkers of AAD provides a reasonable and logical step before proceeding to imaging studies or appropriate therapies. Serum levels of smooth muscle myosin heavy chain and creatine kinases were first shown to be correlated to AAD in the 1990s (*Table 1*). Since the first analysis for AAD patients in 2003, the serologic D-dimer test was extensively studied in aortic diseases, and this was included as one of the laboratory test items for AAD in the European guidelines on the diagnosis and treatment of aortic diseases (level of evidence IIa, level of evidence B) (14). A diagnosis of AAD should be included when the serum D-dimer levels exceed the threshold of 0.5 μg/mL (or 2.738 nmol/L) (1). Low serum D-dimer levels may exclude AAD, but not the possibilities of intramural hematoma and penetrating aortic ulcer (14).

D-dimer is the end-product obtained after a cleavage of the fibrin polymer, which is composed of a conglomeration of fibrin monomers containing a central E-domain with

Table 1 Biomarkers beyond FDPs and D-dimers that indicate AAD

Biomarkers	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)/ NPV (%)	PLR/ NLR	Limitations	References
Smooth muscle myosin heavy chain	2.5 ng/mL	90	97	–	30/0.1	Decreased to baseline 24 hrs after symptom onset	(8,9)
C-reactive protein	9.8 mg/mL†	83	80	NA	NA	Interfered by other inflammatory conditions	(10)
Calponin	2.3 ng/mL* and 159 ng/mL**	50*/63**	87*/73**	56*, 44**/84*, 86**	NA	For initial 6 hrs after symptom onset	(11)
Elastin degradation products	>3 SD above mean values for healthy controls	88.9	99.8	94.1/98.1	NA	Increased baseline yields with age, negative in completely thrombosed dissection	(4,12)
MMP-8	3.6 ng/mL	100	9.5	NA/100	NA	Plasma level, elevated in inflammatory condition	(13)

Data for TGFβ, CK-BB, tenascin-C, and genetic markers are yet to be determined. †, For prediction of in-hospital mortality; *, for acidic isoform; **, for basic isoform. PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; SD, standard deviation; CK-BB, creatine kinase-BB isoform; MMP-8, matrix metalloproteinase-8; TGFβ, transforming growth factor β; NA, not available.

two distal D-domains (*Figure 1A*) (15). When tissue injury occurs, platelets, in combination with the coagulation cascade, are activated. The soluble protein fibrinogen is thereby converted to an insoluble protein fibrin monomer by thrombin, an enzyme product that is generated from the coagulation cascade. Fibrin monomers then aggregate to form fibrin protofibrils through non-enzymatic associations, which are further consolidated by coagulation factor XIIIa, in order to form a cross-linked fibrin polymer (*Figure 1B*). Fibrin cleavage is a repeated step of digestion that occurs at specific sites with the help of plasmin, an activated form of plasminogen present in the interstitial spaces of organs including vascular tissue (15). The degradation products are variable in size, or molecular weight, and are generally called fibrin degradation products (FDP). The terminal FDPs are the D-D-E domain fragments, namely D-dimers (*Figure 1B*). Commercially available kits for D-dimer tests target not only D-D-E fragments but also FDP with D-dimer antigens (16). Under certain pathological conditions, such as disseminated intravascular coagulopathy, fibrinogen is degraded through plasmin before being activated into fibrin monomers. The degradation products include the fragments of D and E-domain molecules, not D-dimers. Commercially available FDP kits detect degradation fragments from both fibrin clots and fibrinogen.

On March 06, 2017, in the issue of *Scientific Reports* (17), Dong *et al.* shared the results of a retrospective study to differentiate AAD patients (n=202) from non-AAD and healthy controls by using circulating levels of FDP and D-dimers, which were measured through latex immunoturbidimetric assays. The diagnosis for the non-AAD group included myocardial infarction (n=45), pulmonary infarction (n=51), and abdominal aortic aneurysm (n=54). The significantly low fibrinogen levels in the AAD and non-AAD groups corresponded with the findings of high FDP and D-dimer levels. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was around 0.66 for both FDP and D-dimer so as to differentiate between AAD and non-AAD patients. The AUC for the ROC curve was around 0.86 for both FDP and D-dimer to differentiate the AAD patients from healthy controls. Dong *et al.* did not list the cut-off values for such differentiation in the study. Previous meta-analyses suggested a threshold of 0.5 μg/mL using D-dimer, which showed a pooled sensitivity of 98% and specificity of 42% (18,19). However, the positive predictive value is generally under 50% at the 0.5 μg/mL threshold of D-dimer levels due to the low prevalence rate of AAD in the emergency departments (19). Hagiwara *et al.* proposed a D-dimer plasma level ≥3.8 μg/mL or FDP ≥12.6 μg/mL for the consideration of a chest CT with contrast (20). The threshold should be lowered for AAD patients with complete thrombosis in the false lumen (20). In addition, Hagiwara *et al.* found a strong correlation (R^2 =0.97) between D-dimer and FDP data, implicating that D-dimer might be representative of FDP in an AAD population, and vice versa (20). D-dimer, rather than FDP,

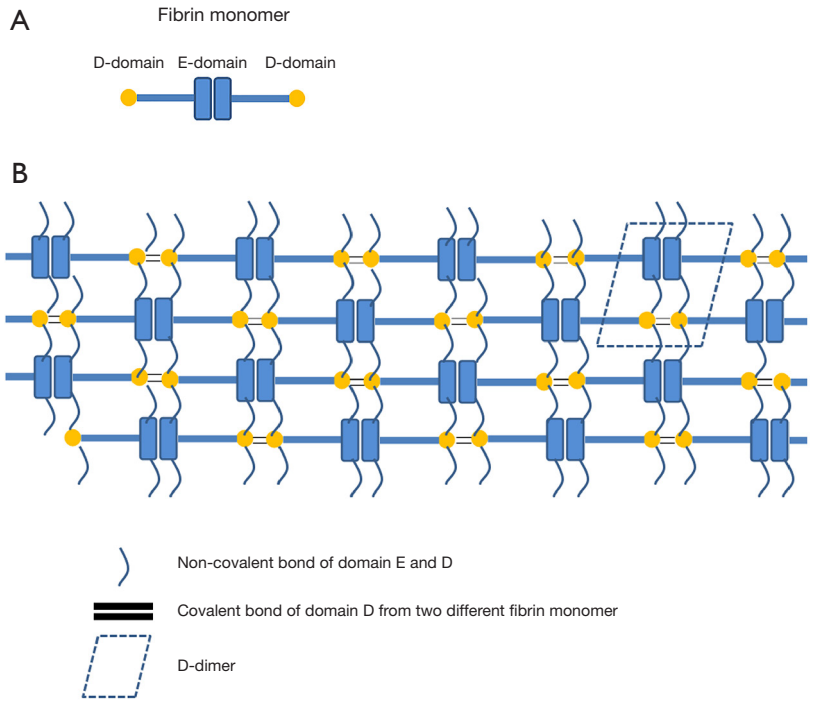

Figure 1 Simplified diagram of fibrin and D-dimer. (A) The fibrin monomer is activated after cleavage of specific peptides in the E-domain by thrombin; (B) when fibrinolysis occurs, plasmin degrades multiple sites of the polymer, thereby sparing the covalent bonds of the intermolecular D-D-domain and the noncovalent linkage of the E-domain to D-D. The molecule that is bound by the parallelogram is the terminal product of fibrinolysis, the D-dimer. Those intermediate products during fibrinolysis are called fibrin degradation products.

is commonly used to rule-out AAD in clinical settings.

In spite of the high sensitivity and AUC data in the above mentioned studies, Moysidis T *et al.* found that the chances of an elevated D-dimer value were lower than 30% among the patients who had chest pain of non-cardiac origin (21). It is generally recommended that D-dimer should be used in conjunction with clinical presentation to diagnose AAD (14,18,21). The American Heart Association provided a risk score that was based on prior medical history, clinical symptoms, and physical examination findings (14,18). The risk score assists in determining the use of D-dimer and imaging studies for the diagnosis of AAD. The diagnostic pathway using systemic D-dimer screening for AAD, without consideration of other clinical information, among patients with chest pain had resulted in a nearly 40% increase of the CT images which were negative for AAD (21). It should also be noted that the baseline D-dimer level is increased with age, and among pregnant cases (15). Nevertheless, all the above-mentioned studies consisted of over 60% male patients, an inevitable gender bias for AAD. Consequently, FDP and D-dimer biomarkers should be used with caution for females and the elderly (>70 years) patients (15). Other potential markers such as smooth muscle myosin, matrix metalloproteinase (14), elastin degradation products, transforming growth factor-β, and tenascin-C were still under investigation and had not been applied clinically (*Table 1*). Newly explored markers such as microRNA (miR-21-5p) and growth factor genes might also shed some new light on early detection of AAD among the patients with non-classical symptoms (22).

In summary, D-dimer or FDP tests could be considered for those with low probability of AAD, at least within 48 hours after the symptom onset. However, negative test results should not preclude the need for a subsequent imaging survey. It is as yet unclear whether D-dimer or FDP tests can shorten the time taken to diagnose AAD. New diagnostic biomarkers are under investigation, and they may be promising. An efficient way to identify AAD from variable and atypical symptoms is to stay updated with comprehensive knowledge about the disease with a respectful mind.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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