Journal of Blood Disorders, Symptoms & Treatments

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Letter to the Editors-in-Chief

A Call for Standardization and Age Adjusted D-dimer Cut-off Value

This article was published in the following Scient Open Access Journal:
Journal of Blood Disorders, Symptoms & Treatments
Received June 07, 2017; **Accepted** July 07, 2017; **Published** July 14, 2017

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D-dimer, a high molecular weight fibrinogen derivative derived from the cleavage of cross-linked fibrin, reflects both thrombin production and activation of fibrinolysis and is a biomarker of thrombosis. It is generated through fibrinolysis during which fibrin polymers are cleaved by circulating enzyme plasmin. Therefore, D-dimer level may be influenced by coagulation, fibrinolysis, or regulatory factors of these processes. In previous studies, higher plasma D-dimer concentration correlated with higher levels of coagulation and inflammatory markers, such as fibrinogen, factor VIII coagulant activity, C-reactive protein, interleukin-6, and with carriage of the factor V (F5) Leiden polymorphism [1,2]. Also, D-dimer has been shown to be associated with the risk of several diseases in prospective studies, including cardiovascular disease and first/recurrent venous thromboembolism [3-5]. Although multiple studies have demonstrated an association between elevated D-dimer and prognosis, no single cut-point has been identified which consistently optimizes the prognostic value of the biomarker. The cut-point evaluated in multiple studies is that which exceeds the conventional D-dimer cut-off value (500 ng/mL). However, the threshold for D-dimer exceeded 5,500 ng/mL in one study [1].

Two dominant issues remain problematic in D-dimer testing: (i) the current lack of uniformity in the type and magnitude of units used for reporting results, and (ii) the lack of a calibrator that can be used to standardize the many assays currently in use [6]. Reviewing recent proficiency testing data reveals that laboratories are reporting fibrinogen equivalent units (FEU) and D-dimer units (DDU) with about equal frequency [1,6]. In addition, the magnitude of units (ng/mL, μg/mL, μg/L, etc.) is also widely variable. This variance was further highlighted by a recent global survey that identified the use of 28 different combinations of measurement units currently used to report D-dimer results worldwide. It is also commonplace for peer-reviewed literature to fail in defining the type of units used in the study. The obvious result of this confusion is that those reading the literature and caring for patients become confused regarding threshold levels and test interpretation. Therefore, there is a strong need for development of a uniform type and magnitude of units for reporting D-dimer data. It is also relevant to highlight that D-dimer results should be interpreted in relation to the clinical indication and the reference values should be adapted in relation to the age.

Another concern is lack of standardization [1-6]. An important aspect is related to the still unmet standardization of the analytical techniques used for D-dimer measurement, which mostly entail enzymatic or latex enhanced turbid metric immunoassays. As previously explained, D-dimer is not a single molecule, but a heterogeneous mix of FDPs containing cross-linked D–D domains. This explains why a universal standard has not been successfully produced so far, and especially why commercial methods, using different monoclonal antibodies against the D-D domain, display imperfect correlations. There are numerous versions for each assay, and clinical investigations often use different approaches, and the assay sensitivity strongly depends on the protocol used. Therefore, the results from different papers cited in this opinion might be difficult to interpret and to reproduce. The current attempts at standardization for some of the better established global assays such as thrombin generation make us hope that this might be resolved in the foreseeable future. We conclude that existing global assays have a potential to be an important tool of hyper coagulation diagnostics. However, their lack of standardization currently impedes their application: different assays and different modifications of each assay vary in their sensitivity and specificity for each specific pathology. In addition, it remains to be seen

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how their sensitivity to hyper coagulation (even when they can reliably detect groups with different risk of thrombosis) can be used for clinical decisions: the risk difference between such groups is statistically significant, but not large.

Moreover, D-dimer is also influenced by age [2,6-8] and concomitant medical conditions, such as atrial fibrillation, heart failure, peripheral artery disease and renal failure [1,2,9-11]. The elevation of D-dimer in these patient groups is a limitation for both the diagnostic and prognostic role of D-dimer, particularly among the elderly and patients with renal failure among whom prolonged VTE prophylaxis can be problematic due to excess inadvertent bleeding [2]. The relationship between D-dimer and aging was indeed predictable as already reported in previous investigations [1-8], and the adoption of age-specific cut-off values may hence be a reasonable approach to increase its diagnostic specificity. It is also conceivable that the use of age-specific cut-offs, higher than the traditional diagnostic thresholds, may be advantageous for diagnosing venous thromboembolism (VTE) in older patients [1,2]. However, D-dimer concentrations increase with age, which leads to a high proportion of older patients with D-dimer concentrations higher than conventional cut-off values .This in turn leads to a low specificity (that is, more false positive results) of D-dimer testing in older patients suspected of having venous thromboembolism.

In conclusion, the use of age-adjusted cutoffs should be further promoted for improving the clinical usefulness of D-dimer testing especially in elderly patients with no high clinical probability and the introduction of a widespread standardization of D-dimer reporting also carries many challenges and some mindful drawbacks.

Conflict of Interest Statement

Nothing to report.

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