D-dimer: Past, present, and future

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The D-dimer level is a measure of clot formation and lysis that results from the degradation of cross-linked fibrin. Widely used as an indicator for the presence of disseminated intravascular coagulation, it's more sensitive than usual measures, such as activated partial thromboplastin time and prothrombin time (PT) [1].

D-dimer also has been established as a rule-out test for venous thromboembolism (VTE). In the outpatient setting, a negative D-dimer, accompanied by a low clinical probability rating (using a tool such as the Wells criteria), indicates that the overall clinical risk of the patient having a VTE is extremely low [2].

Historical use

The usefulness of D-dimer testing as a diagnostic tool lies in its negative predictive value, and research has established its high sensitivity, but low specificity [3]. Testing products can correctly identify D-dimer elevation, but they don't identify why D-dimer is elevated.

Two classes of D-dimer testing methods reporting high negative predictive values are enzyme-linked immunosorbent assay (ELISA) D-dimer and microlatex agglutination [4].

The British Thoracic Society guidelines incorporate "the most investigated assays—a whole-blood red cell agglutination assay (SimpliRED; Agen Biomedical, Brisbane, Australia) and a rapid ELISA (VIDAS; BioMerieux, L'Etoile, France)" [5].

In summary, a negative D-dimer correlated with a low clinical predictive value suggests that VTE isn't present [2]. A negative D-dimer in conjunction with a low clinical probability offers clinicians a convenient and cost-effective diagnostic alternative to more expensive or invasive tests, such as a pulmonary angiogram (for outpatients).

Conversely, the positive predictive value of D-dimer for VTE is quite poor. Many clinical conditions can cause elevated D-dimer levels, so a positive value doesn't identify the specific cause of the elevation. The clinician can't diagnose VTE on positive D-dimer alone. (See What's normal?)

Healthy patients

In healthy patients, procoagulant and anticoagulant factors in the clotting cascade are in fine balance. Any change in the balance could place a patient at risk for VTE or bleeding.

A recent study found that at certain levels, procoagulant and anticoagulant factors are grouped together in the coagulation cascade [6].

Investigators believe the discovery of hereditarily high levels of certain coagulation factors is associated with increased risk of VTE, and regulatory genes may be located outside clotting factor genes that control protein levels affecting the coagulation cascade.

At certain levels, researchers theorize that these regulatory proteins cause grouping together, or clustering, of procoagulant and anticoagulant factors [6]. Procoagulant vitamin K-dependent factors, factor XI, and factor XII were found to cluster together.

Factor V and factor VIII were found to cluster with fibrinogen and D-dimer; factor XIII remained independent. The anticoagulant factors protein C, protein S, and antithrombin also clustered together [6].

Activation of the clotting cascade by a number of clinical conditions, such as endothelial injury, cancer, pregnancy, surgery, sepsis, acute respiratory distress syndrome (ARDS), and trauma, will affect D-dimer results.

Hospitalized patients

If D-dimer can be used as a rule-out tool for VTE in outpatients, why isn't it used more often in the inpatient setting? Some studies have examined the use of D-dimer in the inpatient population, and the consensus is that D-dimer isn't a reliable rule-out tool for VTE in this population.

One study cautioned against the use of D-dimer testing on inpatients due to the high rate of false-positive results in patients with active disease processes such as pneumonia, heart failure, and malignancy [7].

Researchers further described the possibility of a false-negative result in patients receiving anticoagulation prophylaxis or therapy and in those patients for whom duration of symptoms is unknown or subacute.

Their research showed D-dimer levels had little reliability as a rule-out tool in determining which patients did or didn't have VTE if patients met the following criteria:

- they'd been hospitalized for more than 3 days
- they were over age 60
- they had had high C-reactive protein levels [7].

Researchers did document a relationship between D-dimer and C-reactive protein, supporting a connection between inflammation and thrombosis [7]. For every quartile in which C-reactive protein rises, there's a correlational rise in D-dimer.

The higher the two rise, the less reliable D-dimer's negative predictive value becomes. This correlation implies that as inflammation progresses, the likelihood of thromboembolism increases [7].

D-dimer in the ICU

Proinflammatory states in critically ill hospitalized patients lead to elevated D-dimer levels via cytokine activation of the coagulation cascade and corresponding inhibition of fibrinolysis [8].

Although D-dimer hasn't been shown to be an effective resource to rule out VTE in hospitalized patients, given the correlation of D-dimer to protein C and the inflammatory response, researchers are examining whether D-dimer could be used as a prognostic tool for mortality in the emergency department or intensive care unit (ICU), where activation of the inflammatory response is prominent.

Virchow's triad and the subsequent activation of the clotting cascade through physiologic activity, such as the

inflammatory process, can result in microthrombi, which has been implicated in sepsis, ARDS, and multisystem organ failure [9].

Sepsis mortality is directly related to the number and severity of organs affected. Many studies show coagulation abnormalities emerging before symptom onset in sepsis or shock and baseline elevation of D-dimer levels soon after the onset of the first organ system to be affected [10].

One study defined baseline D-dimer as the D-dimer level the day of admission to the ICU, and the first day of severe sepsis as, "the first calendar day after the onset of the first sepsis-induced organ dysfunction [10]."

Researchers also correlated the degree of abnormal baseline D-dimer to 28-day mortality. Changes in PT and D-dimer were related to 28-day mortality [10].

What's normal?

Though multiple tests are available on the market, no gold standard in which to compare results exists, so there's no "normal" value for D-dimer.

With multiple products available designed to measure D-dimer levels, practitioners must be familiar with the test they're using and the respective manufacturer-recommended parameters.

Tests can be quantitative and reported in numerical units of measure, such as nanograms per milliliter, or they can be nonquantitative, which are reported as positive or negative values.

Quantitative tests provide recommended cutoff levels for positive results and units of measure such as nanograms per milliliter, milligrams per liter of fibrinogen equivalent units (FEUs), or D-dimer units. Units of measure aren't interchangeable between testing products, as each product will have its own parameters.

Nonquantitative or semi-quantitative tests rely on reader interpretation and can vary from technician to technician. For example, one study used two types of D-dimer testing products to evaluate the efficacy of D-dimer testing on inpatients versus outpatients.

Although they were both measured in milligrams per liter of FEU, one product reported positive results as greater than 1.0 mg/L and the other reported positive results as greater than 4.0 mg/L [4].

Though each testing kit reported positive results quantitative results in milligrams per liter, each retained its own cutoff value for a positive result. Past that positive value, the exact number wasn't reported.

Researchers who evaluated a rapid assay D-dimer test sought to draw a parallel between D-dimer levels and poor outcomes in the critically ill by comparing Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score (SAPS) scores [9].

Their findings show an association between D-dimer levels 24 hours after admission to an ICU and the 48-hour APACHE II and SAPS scores. Significant correlation was discovered between the 48-hour D-dimer level and the 48-hour APACHE II, SAPS, and the organ system failure index [9].

This relationship demonstrates that the value of using D-dimer to predict clinical severity is seen 48 hours after admission to the ICU. Surprisingly, neither the 24-hour nor the 48-hour D-dimer level predicted in-hospital mortality, whereas APACHE II, SAPS, and the organ system failure index did predict mortality.

However, the D-dimer level was capable of predicting the magnitude of organ failure [9]. Therefore, the investigators suggest that D-dimer be used to predict general clinical severity of the critically ill patient.

A particularly interesting point of the study is that the investigators included surgical patients, in whom D-dimer is expected to be elevated postoperatively.

Treating VTE involves preventing clot extension, embolization, and recurrence [8]. The aim of treatment for microembolism is to limit the degree of the inflammatory response, resolve or prevent further embolization, and prevent or repair as much end organ damage as possible.

The PROWESS study, which documents the efficacy of using recombinant human activated protein C to treat severe sepsis, also documents lower D-dimer levels achieved by means of treatment with activated protein C, which correlated to improved survival [8].

Future trends

The use of D-dimer level as a predictor of severity of coagulopathy, inflammatory response, and mortality in the critically ill patient is becoming more widespread. Investigators are examining D-dimer as it relates to other disease states and processes.

Documentation proves that D-dimer levels decline with anticoagulation, and researchers are looking toward predicting survival in patients with chronic atrial fibrillation. High mean baseline D-dimer levels are related to patients with atrial fibrillation who are receiving oral anticoagulation therapy and who had suffered cardiovascular events, including myocardial infarction, peripheral occlusion, stroke, and death [11].

The study also showed that low D-dimer levels and oral anticoagulation therapy were independently correlated to survival, suggesting that a single D-dimer can predict survival over 2 years [11].

Studies also have documented a correlation between D-dimer and severity of community-acquired pneumonia, as well as D-dimer's role in detecting acute aortic dissection and during cardiopulmonary bypass [12-14].

The groundwork has been laid for future research into the correlation of elevated D-dimer to critical outcomes. Uncovering new ways for D-dimer to be used in hospitals has opened a new door in the advancement of caring for critically ill patients.

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