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Review Article

Appraisal of D-dimer: A meta-analysis

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ABSTRACT

D- dimer assays are most widely used in clinical practice to exclude a diagnosis of pulmonary embolism or deep vein thrombosis. D- dimer assays vary in instrumentation, calibration standard, method of capture and antibody used. These differences impose significant influence on the characteristics of the assays during operation. In this review, we have outlined the general properties and limitations of different D-dimer assays and provided clinical perspective on the role of D-dimer test in the diagnosis and prognosis of venous thromboembolism.

1. Introduction

D-Dimer is the initial screening test used to diagnose cases of venous thromboembolism in the emergency department. It is a marker of endogenous fibrinolysis and is detectable in patients with thromboembolic phenomenon. The process of implementing a new D-dimer method in a laboratory, requires a clinical comparison of the “old” assay versus the “new” assay.[1]

The first step by thrombin cleavage exposes a polymerization site on fibrinogen that promotes the binding of fibrinogen or a monomeric fibrin molecule which bind to one another in an overlapping manner to form thick Protofibrils. The complex formed by thrombin, soluble fibrin polymers and plasma factor XIII promotes the formation of factor XIIIa which cross links fibrin monomers via intermolecular isopeptide bonds between lysine and glutamine residues within the protofibrils and the insoluble fibrin gel in the second step of D-dimer formation.[2]

Various molecular weights of fibrin degradation products are produced including the terminal degradation products of cross linked fibrin containing D-dimer and fragment E complex. High-molecular-weight soluble fragments contain the “D-dimer antigen” and are present in patients with Disseminated intra vascular coagulation and other thrombotic disorders.[3]

Comparing D-dimer assays is challenging. D-dimer testing can be adjusted for age as well as non-age. As D-dimer increases naturally in the body with age the chances of false positive results while testing older individuals are high. Age adjusted D-dimer testing will result in proper diagnosis of actual positive cases and will reduce the cost charges for further unnecessary investigations. With a high negative predictive value, D- dimer assay provides a fast cost effective way for treatment of venous thromboembolism patients. We searched the PubMed database and reviewed the articles related to the d-dimer and venous thromboembolism. This article discusses the different types of D-dimer assays, factors influencing D-dimer testing and the value of D-dimer testing in specific populations such as the elderly, pregnant women etc.

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2. Discussion

The various conditions where the increase in D-dimer is to be monitored by the clinicians include:

Physiological causes for raised D-dimer levels include pregnancy, puerperium, increasing age (>65 years), African American heritage, recent trauma, smoking and the postoperative period.[4]

Pathological causes are deep vein thrombosis, pulmonary embolism, thrombosis in atypical sites–upper arms, mesentric, cerebral veins, Arterial thrombosis-Acute Coronary syndrome, Stroke, Peripheral artery disease, Arterial thromboembolism, Intestinal ischemia, Intravascular thrombosis-catheters, Pace-makers, Artificial valves, Microvascular thrombosis-DIC, Atrial fibrillation, LV aneurysm, Congestive Heart failure, Heart thrombus, Acute aortic dissection, Renal disease, Liverdisease, Infections, Malignancy, Pneumonia, sepsis, Pregnancy, Preeclampsia, HELLP syndrome, Alzheimer's disease, Sickle cell disease, Chronic and inflammatory diseases.[4]

2.1. *Types of D-dimer assays*

Standardization of D-dimer results has not been successful as the analyte is not uniform across the different assays. ELISA D-dimer and rapid whole-blood quantitative D-dimer tests of established central laboratory showed sensitivity and negative predictive value (NPV) of 100%. The rapid whole-blood test had greater specificity for venous thromboembolism cases. (73.3% vs. 67.9%), and the positive predictive value was poor for both tests.[5]

The Vitek Immuno-Diagnostic Assay System (VIDAS) ELISA test was found to have a sensitivity of 100% (500 μg/l) for ruling out pulmonary embolism, in the Christopher study.[6]

In a meta-analysis by Di Nisio et al.[7] the accuracy of different D-dimer assays from 113 individual studies were analysed and it confirmed that the ELISA, the micro plate ELISA, and the automated quantitative latex assays have a higher sensitivity and a lower specificity. This helps in excluding the disease at the cost for additional imaging. The studies proved the high negative predictive value of D-dimer testing in patients with suspected venous thromboembolism after a negative D-dimer test for an interval of 3 months.

Studies found D-dimer to be highly sensitive (>95%) in excluding acute VTE at the cutoff value of 500 μg FEU/l.[8] Taira et al. concluded that patients with D-dimer levels <500 ng DDU/ml may not require additional and costly imaging studies .D-dimer testing showed 100% sensitivity and 100% negative predictive value (NPV), and a negative D-dimer safely excluded VTE. However, the test lacked specificity and positive predictive value.[9]

The awareness of the performance characteristics of the particular D-dimer assay in use at any institute is mandatory to the physicians. The institution should use a previously validated assay and the cutoff value used to rule out venous thromboembolism should be confirmed by the clinical laboratory.[10]

Efforts to standardize D-dimer assay results are still in progress since the analyte is not uniform across different assays. Attempts were made to harmonize assay performance through the interconversion of results from various assays. Specific mathematical formulas are being used which is yet to be accepted as universal practice.[11]

Fluorescence endpoint detection assays can detect D-dimer levels between 0 and 1000g/mL with equivalent sensitivity and specificity and advantage of speed with a wide linear range.[12] Immuno filtration based tests further shortened laboratory turnaround times with excellent sensitivity, specificity, negative and positive predictive values comparable with the gold standard ELISA. These tests help in prompt reporting and clinical management as test results are obtained within 2 minutes.[13]

Collaborative efforts between clinicians and laboratory personnel will help in better exclusion of VTE in the patient population. The clinicians should request D-dimer assays in the appropriate clinical context. The laboratories should also use validated assays with reliable and established cut off values as the cut off values are critical for clinical interpretation and decision-making.

2.2. *Comparison of different D-Dimer assays*

2.3. *Assay methods and technical aspects*

D-dimer is detected and quantified in whole blood, plasma, or serum by monoclonal antibodies that recognize specific epitope on cross-linked D-dimer molecules. These are otherwise absent on the D-domain of fibrinogen and fibrin monomers that are non-cross-linked. At least 30 commercial D-dimer assays are available but there are three general types: enzyme-linked immunosorbent assays (ELISA), immuno fluorescent assays, and latex agglutination assays.[16] which have their own specific considerations and limitations reviewed in various studies.

2.4. *Principles of different D-Dimer methods*

2.4.1. *Quantitative latex enhanced immunoturbidimetric immunoassay*

When a plasma containing D-dimer is mixed with the D-dimer latex reagent (suspension of polystyrene latex particles of uniform size coated with a monoclonal anti-D-Dimer antibody) and the reaction buffer (included in the D-dimer kit), the coated latex particles agglutinate. The degree of agglutination is directly proportional to the D-dimer concentration in the sample which is determined by measuring the decrease of the transmitted light at 405 nm.[17]

Table 1: D-dimer assay [14]

Methodology	Unit type	Reported units	DVT Sensitivity	DVT Specificity
Quantitative, latex enhanced immunoturbidimetric immunoassay	FEU	mg/mL or mg/L	100%	45%
Quantitative, time-resolved fluorometry	-	mg/L	98.7%,	64.4%
Enzyme immunoassay, Chemiluminescence	FEU	ng/mL	100%	63.2%
Polystyrene micro particle agglutination assay.	FEU or DDU	-	94-100%	38%
Quantitative ELISA, Sandwich type	FEU	ng/mL	100%	42%

Table 2: Point of care D-dimer assays [14,15]

Methodology	Unit type	Reported units	DVT Sensitivity	DVT Specificity
Fluorescence immunoassay	DDU	ng/mL	97%	48%
Quantitative micro particle enzyme immunoassay, chemiluminescence	FEU	ng/mL	98%	40%
Quantitative latex enhanced immunoturbidimetric immunoassay	FEU	mg/mL	95%	62%
Qualitative, solid- phase immuno chromatography	-	Positive or negative	99%	53%
Qualitative or semi quantitative latex agglutination	-	Positive or negative	96%	92%
Semi-quantitative, immuno filtration	DDU	mg/L	50%	40%
Qualitative, red blood cell agglutination	-	Positive or negative	94%	67%

2.4.2. Quantitative time-resolved fluorometry

When a mixture of fluorescent compounds are irradiated with light of the appropriate frequency, it will be absorbed in about 10-15 seconds. In the process of absorption, the molecules move from ground to the first excited singlet electronic state and emit either short or long-lived fluorescence. [18]

2.4.3. Enzyme immunoassay chemiluminescence

Chemiluminescent Enzyme Immunoassay is based on combined magnetic separation technology and sensitive chemiluminescence analysis with specific antigen-antibody reaction. The complex of enzyme labeled antibody, target antigen in samples and magnetic particle antibody act as a “sandwich” structure in sandwich chemiluminescence enzyme immunoassay. The complex are segregated and the luminescent substrate is added to generate glow light. As the luminous intensity is proportional to the target antigen level in the sample, the target antigen can be measured. [19]

2.4.4. Polystyrene microparticle agglutination assay

In these immunoassays, Latex or polystyrene microparticles coated with monoclonal or polyclonal antibodies react with at least two non-overlapping epitopes of the D-dimer. These antibody coated particles are introduced to a sample which may be diluted in a reaction buffer. The antibody-coated particles agglutinate and initiates a light scattering event which is detected by the analyser. [20]

2.4.5. Quantitative sandwich ELISA

A target-specific antibody pre-coated in the wells of the supplied micro plates is used with samples, standards, or controls added into these wells bound to the immobilized (capture) antibody. The sandwich is formed by the addition of the second (detector) antibody, a substrate solution is added that reacts with the enzyme-antibody-target complex to produce measurable signal which is directly proportional to the concentration of target present in the original specimen. [21]

2.4.6. *Point of care techniques*

2.4.6.1. Fluorescence immunoassay. Whole blood mixed with fluorescent-labeled anti-D-dimer detector antibody is loaded onto a disposable cartridge. The fluorescent intensity after 12 min of incubation is measured by scanning of test cartridge and converted as level of D-dimer in a laser fluorescent scanner.[22]

2.4.6.2. Quantitative microparticle enzyme immunoassay, chemiluminescence. (MEIA) is a technique in which the solid-phase support consists of very small microparticles in liquid suspension. Specific reagent antibodies are covalently bound to the microparticles. Antigen, if present, is then "sandwiched" between bound antibodies and antigen-specific, enzyme- labeled antibodies. Unbound material is washed through the glass-fiber matrix into an absorbent, opaque blotter below, using pre-warmed buffer.[23]

2.4.6.3. Qualitative solid- phase immuno-chromatography. This assay use a porous solid support within which the sample and the reagents migrate by capillary diffusion. The presence of the analyte in the sample is thus measured through the detection of the labelled reagent.[24]

2.4.6.4. Semi-quantitative immunofiltration. Liquid flow technology is used and a porous nitrocellulose membrane is employed as a solid support to immobilize the analyte of interest, with a proper signaling system in a typical sandwich reaction. Traditional IFAs are commonly qualitative or semi-quantitative and have limitations in efficient testing of samples in field diagnostics.[25]

2.4.6.5. Qualitative red blood cell agglutination. It is a unique whole-blood assay that uses a bispecific antibody to human red blood cells and D dimer. Presence of elevated levels of D dimer (>0.2 g/mL) in a whole-blood sample will cause visible agglutination of red blood cells by this antibody.[26]

3. Limitations of assay of D-dimer

3.1. *Lack of a reference standard*

Lack of a reference standard makes a direct comparison of different D-dimer assays impossible as most laboratory assays are validated against a reference standard. Developing a reference standard is difficult and various D-dimer studies confirm that they are not inter-changeable.[27]

In some observational study, eligible patients with ages 50 and older with symptoms of PE underwent D-dimer testing. Test characteristics of the D-dimer assay were calculated using the standard reference value (500 ng/ml), the local reference value (470 ng/ml), and an age-adjusted threshold (10 ng/ml × patient's age).Limitations are D-dimer elevation in certain clinical scenarios as age, pregnancy, cancer and lack of clinical standardization.[28]

3.2. *Cut off D-dimer values*

The reference concentration for D-dimer is <250ng/ml and the reference range is ideally established by the performing laboratory. If a cut off value published in the literature is used, it has to be determined with the same method from the same manufacturer. Few analysis reported that there is no clear advantage of measuring D-dimer after the age of 80.[29]

3.3. *Factors affecting D-dimer levels*

D-dimer result is well affected by the assay choice, by patient characteristics such as the extent of thrombosis and fibrinolytic activity, duration of symptoms, age, surgical procedures, anticoagulants, and comorbid conditions such as inflammatory states, cancer, pregnancy and the postpartum period, and previous VTE.[30]

A positive correlation between thrombus extension and high D-dimer values in the presence of larger thrombi has been found in studies. An inverse relation with duration between onset of symptoms and testing is established, with 25% of the initial value found after 1-2 weeks.[31] The sensitivity of D-dimer test was inversely correlated to the duration of symptoms.

3.4. *Cancer*

The validity of D-dimer assay in cancer patients is compromised as the levels may be elevated even in the absence of thrombosis.

D-dimer levels >8000 ng FEU/ml is associated with an increased incidence of malignancy[32] Lee et al. assessed D-dimer levels in 1068 patients with suspected DVT and the sensitivity of D-dimer test was found to be 86% and 83% in patients with and without cancer respectively.[33]

3.5. *Pregnancy*

The whole-blood agglutination D-dimer has been evaluated in a prospective study including 149 pregnant women which showed 100% sensitivity, 100% NPV, and a specificity of 60%. The study found that D-dimer measurements were helpful in excluding VTE in the first and second trimester of pregnancy.[34] D-dimer testing had 100% sensitivity at the new cutoff values for the first, second, and third trimesters (286 ng DDU/ml, 457 ng DDU/ml, and 644 ng DDU/ml, respectively) as found in another prospective study.[35]

3.6. *Age*

The concentration of the fibrin degradation product increases with age, hence D-dimer test shows high false positive rate in elderly patients. Adjusting the D-dimer cut-off values to the age of outpatients >50

Table 3: Comparison of D dimer by two different methods

S. No.	D-dimer elite pro Nephelometry ng/ml	D-dimer AU 480 Turbidometry ng/ml after conversion of FEU/ml	Percentage (%) difference
1.	355	325	8.45
2.	291	330	11.8
3.	190	175	7.89
4.	244	475	5.3
5.	291	300	3.09
6.	278	200	28.05
7.	214	150	29.9
8.	286	185	35.3
9.	278	220	20.86
10.	187	65	65.2
11.	280	195	30.3
12.	1187	870	26.7
13.	236	150	36.4
14.	245	485	49.4
15.	210	150	28.5
16.	348	295	15.2
17.	288	300	4
18.	188	150	20.2
19.	213	200	6.1
20.	192	235	18.2

years is required as it increases specificity.[36]

3.7. *Pre-analytical variables*

3.7.1. *Sample collection*

Use of straight needles with 19 to 22 gauge (G) diameter is recommended.

Excess vein manipulation with the needle should be avoided to limit the risk of developing clots as it has been found to potentially impact D-dimer concentration.[37] Samples should be delivered to the laboratory at ambient temperature (15–22 °C), usually <1 hour after collection.[38]

3.7.2. *Tube material*

Silicone-coated glass or poly-propylene plastic is preferred as these are non-activating material and prevents initiation of clotting due to false hemostasis activation in the blood collection tube.[37]

3.7.3. *Anticoagulant sample*

Collection tubes containing 3.2%buffered sodium citrate anticoagulants are recommended by the Clinical Laboratory Standards Institute (CLSI) for the majority of hemostasis tests.[37]

A blood to anticoagulant ratio of 9:1 is recommended because the sodium citrate anticoagulant can be used only in a liquid form. Failure to correctly fill the citrate anticoagulant tube may also lead to underestimating D-dimer and fibrinogen.[39] Hence, the sample should be checked for clotting, under filling, or overfilling.

Tourniquet should be removed as soon as the needle is in the vein and it should not remain in place for more than 1–2 min. D-dimer values significantly increased by 13.4%, when measured in samples collected after 3 min of venous stasis as mentioned in Lippi et al.[40]

3.8. *Post-analytical variables*

3.8.1. *Different units*

The use of different units (FEU or DDU)causes confusion and is challenging for clinicians which may potentially lead to misdiagnosis of patients.[41]

3.8.2. *Turnaround time (TAT)*

The TAT is a crucial aspect in D-dimer reporting and an overall TAT<1 h, seems suitable for managing the majority of urgent test requests.[42]

3.8.3. *Interfering substances*

Paraproteinemia, icterus, lipemia, and hemolysis are the common types of interferences in the preanalytical phase of D-dimer testing.

A significant increase in D-dimer level could be observed in samples containing a final whole blood lysate concentration of at least 2.7% obtained with a freeze-thaw cycle (-70degreeC) as mentioned in Lippi et al.[43]

3.9. *Application of D-Dimer in COVID-19*

D-dimer has been helpful in predicting the prognosis in COVID-19 patients. Reports suggests that 50% of patients who had increased D-dimer levels(greater than 2 micro gm/ml) at admission were associated with poor prognosis and increased mortality in Covid-19 patients from Wuhan.[44]

SARS-CoV-2 has propensity for endothelium and lungs thus brings about prothrombotic changes related to ARDS.[45]

According to Wu et al.[46] COVID-19 patients with ARDS had significantly higher D-dimer levels. Also, patients who died of ARDS had higher D-dimer levels than who survived. A notable relation was found between D-dimer elevation, development of ARDS and progression to death.

D-dimer may be useful as a point of care test in the COVID-19 management. Patients treated with convalescent plasma therapy in China showed decreased D-dimer levels, thus it can be used for monitoring therapy and outcome.[47] Also D-dimer cut-off levels can be used to determine the dose in anticoagulation therapy as early intervention since relationship exist between D-dimer and severity of COVID-19.[48]

4. Conclusion

Clinicians should be aware of the various performance characteristics and limitations of the available assays to make accurate and on time therapeutic decisions. Standardization and understanding of assay performance characteristics of different D-dimer assays will help to efficiently utilize this test. Also, further evaluation of the accuracy of age-adjusted D-dimer cut-offs in actual clinical practice should be done. Harmonization of different D-dimer measurements should be achieved by proper discussion among manufacturers, scientists and clinicians.

5. Conflict of Interest

Authors have no conflict of interest to declare.

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None.

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