

D-dimer Testing in COVID-19: From Basics to Clinical Application

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COVID-19 is a highly contagious respiratory tract infection caused by SARS-CoV2, and demonstrates hyper coagulability and hyper fibrinolysis in its severe form. Of the many biomarkers in COVID-19, D-dimer is considered as an important predictor for the severity of the disease. However, it is important to understand the D-dimer itself and to critically appraise the significance of its diagnostic tests in general and in the management of COVID-19, in particular. In this editorial, these issues were addressed.

The understanding for normal haemostasis is constantly evolving and yet more need to be learnt. It is known that fibrinogen is a clotting factor, which is synthesised in liver and is abundantly present in normal plasma. It is a dimer of three polypeptide chains ($A\alpha$, $B\beta$, γ); and each dimer has a central E-domain with two adjoining D-domains. Thrombin, which plays a pivotal role in coagulation cascade, cleaves fibrinopeptides A and B from fibrinogen, leaving fibrin monomer for self-polymerisation and covalent crosslinking by factor XIII, resulting in a firm and stable clot. This fibrin should be promptly removed by the fibrinolytic system to prevent formation of occlusive thrombi. Secretion of tissue plasminogen activator (t-PA) by vascular endothelial cells cleaves plasminogen to plasmin for breaking down fibrin into degradation products (FDPs) of variable sizes, including D-dimers. Hence, D-dimer is the smallest FDP composed of two fibrin molecules; and under normal circumstances, only a small amount is present in the blood. Circulating D-dimer is an indicator of activated intravascular coagulation, formation of cross-linked fibrin and finally its degradation. Besides clotting inside the blood vessels, active fibrinolysis in lungs may contribute in high circulating D-dimers in COVID-19.

It is imperative for a physician to understand D-dimer assays, so that normal results can be differentiated from abnormal ones. The available assays are both qualitative and quantitative; and can be performed in a clinical laboratory or on a point-of-care testing device by using monoclonal antibodies for detecting specific epitopes on cross-linked D-dimer.

The commonly used techniques of D-dimer assays (in whole blood, plasma, or serum) are latex agglutination, enzyme-linked immunosorbent (ELISA) and more recently latex-enhanced immunoturbidimetry, chemiluminescence and immunofluorescent having variable sensitivities, specificities and cut offs.¹ Overall, the D-dimer test is highly sensitive but non-specific as it is increased in a wide variety of physiological conditions (such as aging and pregnancy) and in pathological conditions like infection, inflammation, aortic dissection, trauma, malignancy, recent surgery etc. It is important for the clinicians to know that D-dimer assays are not standardised, the results have high inter-laboratory variation and, therefore, are not interchangeable. Each laboratory should verify/make its own reference range and define decision thresholds for excluding thrombotic conditions. Interpretation of the test results may be confusing for the clinicians as the reported unit may be fibrinogen equivalent unit (FEU/ml) or D-dimer unit (DDU/ml) and the magnitude of unit may be ng/mL, μ g/L, mg/L etc. It is important that unit of D-dimer should be the same as recommended by the manufacturer; and if the units are converted then the laboratory should verify the reported results for the patients.

In practicality, D-dimer assay is clinically useful in conjunction with a validated clinical tool that defines the probability of having venous thromboembolism. Therefore, in a patient with suspected deep venous thrombosis of extremities (DVT) and or pulmonary embolism (PE) having low clinical probability and a D-dimer value below threshold, VTE can be excluded and does not require further imaging for confirmation.² However, as not all D-dimer assays are equally sensitive, laboratories follow recommendations of clinical and laboratory standards institute; whereby, a D-dimer assay should have $\geq 98\%$ negative predictive value (NPV) and $\geq 97\%$ sensitivity to be used for VTE exclusion. In simple terms, a sensitive D-dimer assay can rule out VTE, but should not be used as a single diagnostic modality to rule in VTE. Based on underlying risk factors and global coagulation tests, D-dimer assay is also helpful in the evaluation of disseminated intravascular coagulation (DIC) as per diagnostic scoring system defined by international society of thrombosis and haemostasis (ISTH).³

With this background information of D-dimer assay, one needs to understand its utility in the current pandemic. COVID-19 in its severe form activates coagulation; and there is evidence of SARS-CoV2 direct endothelial injury, resulting in microvascular inflammation with complement activation and storm of

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cytokines leading to COVID-19 associated coagulopathy.⁴ The result is widespread thrombin generation; but in contrast to conventional DIC, patients usually have mild thrombocytopenia, slightly prolonged clotting time and increased fibrinogen,⁵ while D-dimer levels are increased in both the conditions. Rarely, a patient with severe COVID-19 may have overt DIC and multiorgan failure.

In a study on 248 patients admitted with COVID-19 at Wuhan, D-dimer was elevated in 74.6% of the patients; and a D-dimer value of >2.0 mg/L at presentation was associated with a high mortality (OR 10.17; 95% CI 1.10-94.38).⁶ While a rising trend in D-dimer is indicative of disease progression and overall poor survival,⁷ estimating D-dimer in non-hospitalised patients is not warranted. Patients having COVID-19 are at increased risk of having arterial or venous thrombotic events like stroke, myocardial infarction, DVT and PE.⁸ Since patients with severe COVID-19 infections invariably have high D-dimer values and are at risk of VTE as well, the D-dimer alone should not be used to diagnose VTE in such patients. High clinical suspicion and/or imaging (if possible) is required to diagnose a thrombotic event and for initiating therapeutic anticoagulation in these patients, though a D-dimer level of >3000 ng/mL was considered as a valuable screening tool for VTE in COVID-19 by Gibson *et al.* in 2020.⁹ American Society of Hematology considers a normal D-dimer value to effectively exclude DVT/PE in patients having COVID-19. Interestingly, D-dimer remained elevated in convalescent state in 25.3% of 150 patients for 4 months following diagnosis irrespective of their history of hospitalisation; and 8% of them have twice the level of upper limit of normal range.¹⁰ This increase in post-recovery D-dimer value was observed even after normalisation of inflammatory and other coagulation markers, raising the possibility of extravascular pulmonary fibrinolysis as the source of D-dimers.¹⁰ Future studies may indicate the relevance of increased post-COVID D-dimers in long term complications of the disorder.

In conclusion, D-dimer is a useful biomarker for monitoring disease severity, progression, and mortality; and in excluding venous thrombotic events in patients having COVID-19. In all patients, the laboratory results should be evaluated carefully to differentiate normal from subnormal tests. Despite exten-

sive data on D-dimer levels in COVID-19, the present understanding is far from perfect; and as such, much remains to be learnt.

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