D-DIMER

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Background

D-dimer (DD) is a fibrin degradation product, a small protein fragment released in the blood after a blood clot is slowly degraded by fibrinolysis. DD concentration is determined in a lab to diagnose or exclude thrombosis utilizing a DD test to detect often trace concentrations of DD. DD assays vary widely concerning the antibody used, capture method, instrumentation required, and calibration standard, but generally, a positive DD assay can indicate thrombotic issues that may necessitate immediate care. We reviewed the published literature on DD to acquire more information surrounding the significance of elevated DD levels.

What is DD?

D-dimer is a protein fragment from the breakdown of a blood clot. DD is produced when plasmin, an enzyme activated through the fibrinolytic pathway, cleaves fibrin to break down clots. DD consists of two covalently bound fibrin D domains cross-linked by factor XIII when the clot was formed. This fragment forms epitopes targeted by monoclonal antibodies in DD assays to confirm that the coagulation cascade is generating thrombin (Figure 1).

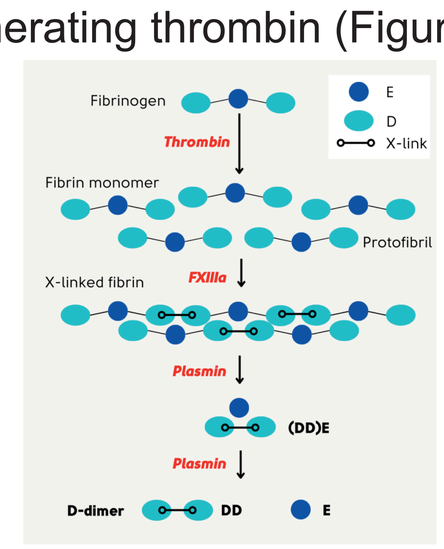

Figure 1: Coagulation Cascade

Methods

DD is not usually detectable in blood; it is produced when blood clots break down. The presence of DD in the blood or urine may indicate the development of a clot. A d-dimer test is done by taking a blood sample from a vein, usually in the arm, using a small needle and blue-topped tube with sodium citrate. The procedure is safe, easy, and usually takes less than five minutes. After the blood sample is collected, it is then sent to a clinical laboratory for testing. If results show higher than normal levels of DD, it may be a sign of a clotting disorder or a blood clot.

Reference Range of DD

D-dimer is a protein released when blood clots break down (Figure 2). A typical range is 0-0.50 milligrams per liter (mg/L) of blood. Levels of 0.50 mg/L or higher may indicate blood clots in the body. DD measurement is a very important step in VTE diagnosis, as it allows clinicians to rule out the disease in around 30% of outpatients with suspected DVT or PE. The test is less useful in elderly patients > 50 years.

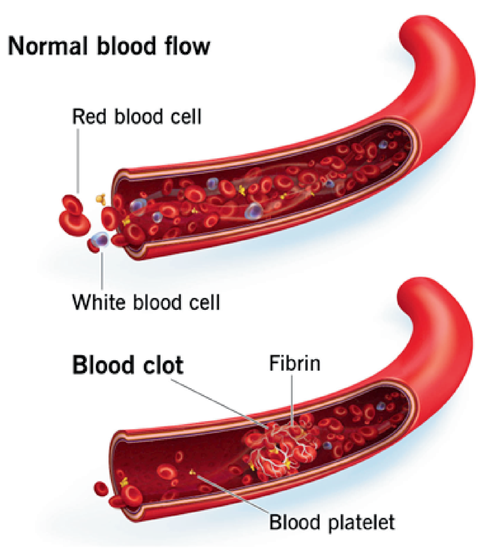

Figure 2: Formation of Blood Clot

Hazard ratio for death by increase in DD

As the DD Levels go up, so does the hazard ratio for death (Table 1).

	D-dimer categories (ng/mL)				
N.	≤221 13,214	222-248 1,483	249-312 1,472	>312 1,470	*P* for trend
Deaths from any cause	48 (1.2%)	60 (1.7%)	49 (2.7%)	123 (4.0%)	
Person-years	55 689	6 190	5 995	5 933	
Crude	-1- (Reference)	1.50 (0.98-2.29)	2.50 (1.77-3.54)	3.60 (2.66-4.87)	<0.0001
Age and sex adjusted	-1- (Reference)	1.19 (0.78-1.82)	1.45 (1.01-2.09)	2.03 (1.48-2.78)	<0.0001
+ risk factors*	-1- (Reference)	1.06 (0.68-1.65)	1.45 (1.00-2.10)	1.97 (1.43-2.72)	<0.0001
+ risk factors*, CRP and WBC	-1- (Reference)	1.01 (0.65-1.58)	1.38 (0.96-2.00)	1.86 (1.35-2.58)	0.0002

**Smoking, body mass index, alcohol intake, and hypertensive, diabetic or dyslipidemic status. CRP: c- reactive protein; WBC: white blood cell count.*

Genetic basis of DD

- 12 single-nucleotide polymorphisms (SNPs) in F5 were significantly associated with DD levels in European Americans.
- One variant of F5, the factor V Leiden F5 R506Q, is associated with an increased risk of arterial and venous thrombosis.
- 3 SNPs in Fibrinogen alpha chain (FGA) were associated with DD levels in European Americans.
- One variant of FGA, the FGA Thr331Ala, is associated with an increased risk of arterial and venous thrombosis.
- African ancestral and sex-specific genetic effects of the F3 and HBB loci may contribute to higher D-dimer levels in African American women.
- Single-nucleotide polymorphisms (SNPs) in Fibrinogen gamma chain (FGG), FGA, and F5 mediate increases in DD (Figure 3)

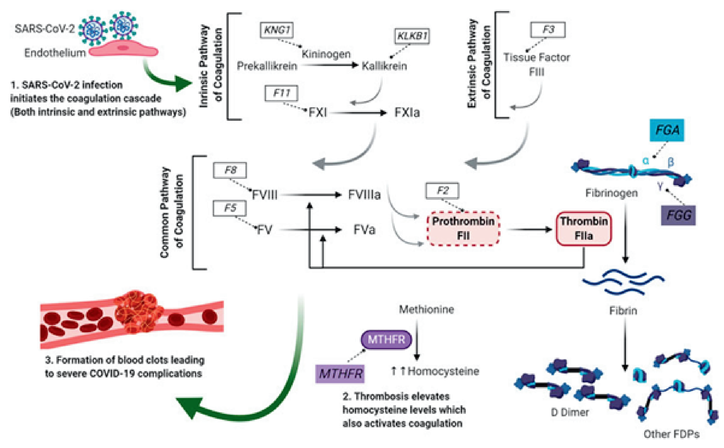

Figure 3: SNPs in FGG, FGA, and F5

Conduct of DD Test

- False negative results are often obtained following administration of the following: Aspirin, Clopidogrel, Ticagrelor, Statins.

Laboratory testing of DD

A DD test measures the amount of D-dimer in the blood. DD is a protein fragment that's created when a blood clot dissolves. DD is ordered for suspected cases of DVT, PE, or stroke. A positive test result indicates that DD levels are higher than normal, which suggests a blood clot or blood clotting problems might be present. The American Board of Internal Medicine defines a negative D-dimer level as below 0.50 milligrams per liter (mg/L) fibrinogen equivalent units (FEU), and positive if it's above 0.50 mg/L FEU. There's no standard measurement scale for this test, so a doctor will explain what the readings mean for the specific test.

Conclusions

DD is produced when plasmin cleaves fibrin to break down clots. DD is valuable for blood clot detection. High DD levels can indicate DVT or PE, but the presence of DD cannot tell the clot's location. Pregnancy, cancer, and old age cause elevated DD. Aspirin and statins give false negative results.

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