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PATHCHAT

Dr Pamela Moodley
Consultant Haematologist, Ampath Laboratories

Clinical Use of the D-dimer Assay

What are D-dimers?

- D-dimer is a marker of fibrinolysis.
- Coagulation results in the formation of the fibrin clot.
- Fibrinolysis is the subsequent degradation of the fibrin clot.
- D-dimer is a protein that is released into the circulation during the process of fibrin clot breakdown.
- It is a specific product of cross-linked fibrin degradation by plasmin.

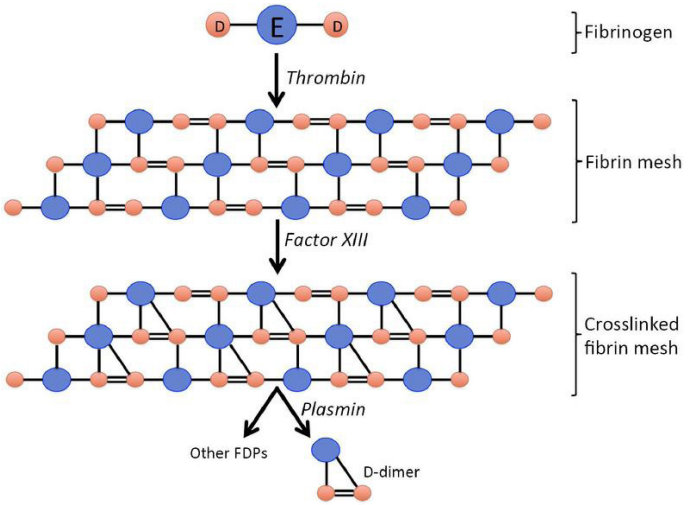


Figure: 1
[From: Wikimedia Commons, the free media repository]

Fibrin degradation is formed by the sequential action of three enzymes: thrombin, factor XIIIa and plasmin. Thrombin cleaves fibrinogen-producing fibrin monomers that aggregate into proteofibrils (fibrin mesh). Factor XIII then cross-links the fibrin proteofibrils at the D fragment site leading to cross-linked fibrin. Plasmin degrades the cross-linked fibrin to release fibrin degradation products (FDPs) and the D-dimer antigen.

Clinical aspects

- Measurement of D-dimer may indicate a disturbance of the balance between the two processes of coagulation and fibrinolysis.

Clinical applications

D-dimer measurement has been validated in the following:

- The exclusion of venous thromboembolism (VTE) in certain patient populations:
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Prediction of recurrent VTE and risk stratification of patients for VTE recurrence
- Diagnosis and monitoring of disseminated intravascular coagulation (DIC)

Choice of D-dimer test

At AMPATH we use an assay that uses the principle of Enzyme-linked-immunosorbent-assay (ELISA).

It meets the following criteria:

- Cut-off determined by clinical studies.
- High sensitivity ***(high predictive negative value)*** and acceptable specificity.
- Access available 24 hours a day, 7 days a week.
- Rapid turnaround time: less than one hour.
- Quantitative results.

Patient and sample collection

- Avoid trauma or stasis when venesecting.
- Collect sample into a citrate tube (blue top).
- Tube must be adequately filled (minimum 4 mℓ).
- Sample is stable for up to 24 hours at room temperature.

Reference range

- Normal range: <0.50mg/l (ug/ml=mg/l).

D-dimer as a diagnostic tool

- It has a ***high negative predictive value*** for the diagnosis of VTE, especially if used in combination with the pre-test clinical probability.
- In low-risk patients, the absence of elevated D-dimer virtually "rules out" thrombosis-negative predictive value.
- It has been shown to have the most reliable negative predictive value when used to exclude DVT in younger patients, without co-morbidity, previous history of VTE and with a short duration of symptoms.
- In this scenario, it helps to eliminate unnecessary tests, venograms or lung scans and is an efficient cost-effective strategy to screen and manage patients.
- The presence of D-dimer cannot "rule in" a diagnosis - positive predictive value.

Limitations

False positive	False negative
Recent surgery	Symptoms older than 7–10 days
Haemorrhage	Patient started on therapeutic heparin or oral anticoagulation
Trauma	Children
Malignancy	Small or insufficient clot size
Sepsis and severe infection	Distal DVT
Advanced age ± co-morbidity	Upper extremity DVT
Pregnancy	Hypofibrinolysis
Liver disease	

D-dimer and disseminated intravascular coagulation (DIC)

- DIC is a complex syndrome, secondary to several underlying disorders, leading to the following:
  - Activation of coagulation and fibrinolysis
  - Consumption of platelets and coagulation factors
- The diagnosis of DIC should encompass both clinical and laboratory information.
- The DIC scoring system of the International Society for Thrombosis and Haemostasis (ISTH) provides an objective measurement of DIC.

ISTH diagnostic scoring system for DIC

- Scoring system for overt DIC.
- Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
- If yes: Proceed. If no: Do not use this algorithm.
- Order coagulation tests and score the tests.

Laboratory test	Result	Score
Platelet count ($10^9/\ell$)	>100 50–100 <50	0 1 2
Fibrin marker, e.g. D-dimer	None Moderate increase Strong increase	0 2 3
Prolonged prothrombin time (PT)	<3 3–5.9 >6	0 1 2
Fibrinogen level	>1g/dℓ <1g/dℓ	0 1

Calculate score:

- >5 compatible with overt DIC: repeat score daily.
- <5 suggestive of non-overt DIC: repeat score in one or two days.

D-dimer and venous thromboembolism

Upon presentation, all patients should be carefully evaluated for clinical pretest probability of VTE using a validated clinical prediction rule (CPR) and then stratified into clinical probability groups: low, intermediate and high. The Wells prediction rules for DVT and for pulmonary embolism have been validated and are frequently used to estimate the probability of VTE before performing more definitive testing on patients. It is important to note that D-dimer levels are commonly elevated for various reasons in hospitalised patients.

Table 1: Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Model for Predicting Pre-test Probability of Deep Vein Thrombosis

Clinical characteristics	Score
Malignancy	1
Paralysis, paresis, plaster on lower extremities	1
Bed-ridden >3 days, major surgery < 12 weeks	1
Local tenderness along deep vein system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic leg	1
Pitting oedema on symptomatic leg	1
Collateral superficial veins	1
Alternative diagnosis at least as likely as DVT	-2
If both legs are symptomatic, score the more severe side.	
Clinical probability	**Total**
Low	< 1
Intermediate	1-2
High	> 2

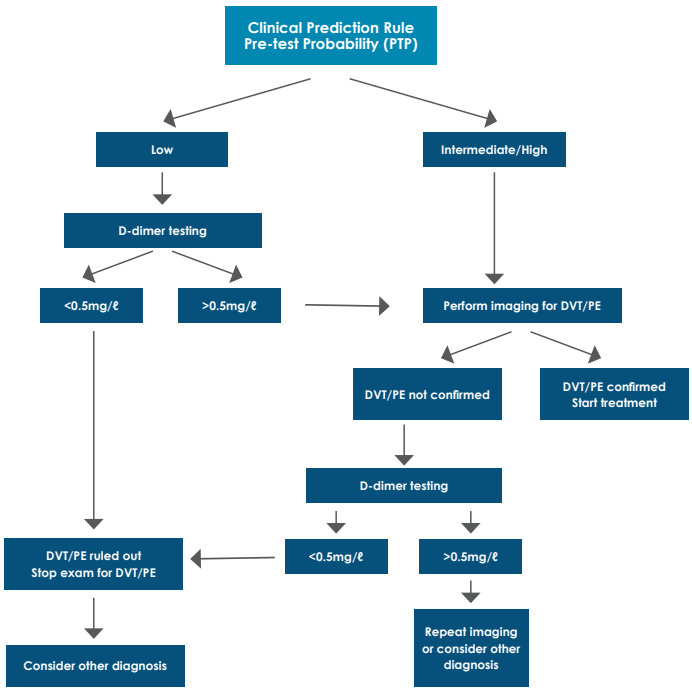
Table 2: Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Model for Predicting Pre-test Probability of Pulmonary Embolism

Clinical characteristics	Score
Clinical signs and symptoms of DVT	3
Alternative less likely than PE	3
Heart rate >100 beats per minute	1.5
Recent surgery or immobilisation	1.5
Previous DVT or PE	1.5
Haemoptysis	1.0
Malignancy	1.0
Clinical probability	**Total**
Low	< 2
Intermediate	2-6
High	> 6

Table 3: Methods available for diagnostic work-up of deep vein thrombosis (DVT) and pulmonary embolus (PE)

Method	Deep vein thrombosis	Pulmonary embolus
Clinical	Clinical pre-test probability	Clinical pret-est probability
Laboratory test	D-dimer	D-dimer
Non-invasive	Compression ultrasound (CUS)	Perfusion-ventilation (V-Q scan)
	Serial ultrasound	Spiral CT
	Impedance plethysmography	MRI
Invasive	Constrast venography	Pulmonary angiography

Diagnostic algorithm for deep vein thrombosis and pulmonary embolus



Discussion

D-dimer should not be used as a stand-alone test to exclude/confirm venous thromboembolism.

Evidence supports the use of clinical prediction rules to establish pretest probablity of VTE before further testing can be done.

A negative D-dimer test in patients with a low pretest probability of VTE is sufficient to exlude VTE and prevent unnecessary testing.

D-dimer levels as a determinant of recurrence risk

- Current evidence suggests that quantitative D-dimer assays measured at the end of wafarin therapy and then one month after its discontinuation can help determine the recurrence risk.
- Warfarin reduces thrombin generation in vivo, resulting in decreased D-dimer levels.
- A negative D-dimer test was associated with lower annual risk of recurrence than a positive D-dimer test.
- D-dimer therefore appears to be a useful biomarker in evaluating recurrence risk and should be used in context along with consideration of individual risk factors for recurrence, risk of bleeding and individual patient preferences.

References

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