Original article

The use of D-dimer in exclusion of diagnosis of suspected Deep Vein Thrombosis

Lamyaa Jaafar Hammoodi Alqaisi [1], Hussein Hasan Abed [2], Rasha Tariq Jawad [3]

(1)M.B.Ch.B, F.I.C.M.S.\Hemopathology, Senior Specialist Hemopathologist, Manager of Laboratory Department of Ibn Albitar Cardiac Specialized Center, Baghdad, Iraq.

(2) M.B.Ch.B, F.I.C.M.S.\Cardiovascular Surgery, Senior Specialist Surgeon, Manager of Perfusion Department of Ibn Albitar Cardiac Specialized Center, Baghdad, Iraq.

(3) M.B.Ch.B, F.I.C.M.S.\Hemopathology, Senior Specialist Hemopathologist, Manager of Laboratory Department of Central Child Teaching, Baghdad, Iraq.

ABSTRACT

Background: Deep venous thrombosis is a common disorder associated with significant morbidity, chronic venous insufficiency as well as fatal pulmonary embolism. venography has been the gold standard of diagnosis, however it has been replaced in most areas by duplex ultrasound which is generally very good method .An interesting new approach to the diagnosis of DVT is D-dimer testing, D-dimer levels reflect the amount of lysed, crossed-linked fibrin and may be useful diagnostic marker in the clinically suspected DVT .D-dimer can be measured either quantitatively by ELISA or qualitatively by latex agglutination.

Objectives: The aim of the study was to evaluate the use of D-dimer in exclusion of the diagnosis of DVT.

Patient and methods: A total of 50 patients presented to vascular outpatient department with clinical suspicion of DVT have been studied ,patients with old DVT ,patients on anticoagulant, and patient with severe infection or inflammation were excluded .Venous duplex ultrasonography of the affected limb or limbs was done and citrated blood sample was analyzed for D-dimer by a VIDAS method for all patients blindly to the results of venous duplex .Sensitivity ,specificity ,negative and positive predictive values were calculated .ROC curve then was generated from sensitivity and 1 _ specificity values at a continuum of D-dimer level to determine the optimal cut-off level of VIDAS D-dimer for exclusion of DVT.

Results: The mean age of DVT group was 43 year. DVT was confirmed in 37 patients (74%), and excluded in 13 patients (26%) by venous duplex .The mean D-dimer level in the DVT group was 5498.021ng/dl while in non DVT group was 1906.384ng/dl this difference was statistically significant (P=0.0003). The sensitivity , specificity , negative and positive predictive values of VIDAS method at cut-off points(500 and 900) ng/dl were (100% , 33% , 100% , 82%) respectively ,and at 3000ng/dl (71% ,75%, 47%,90%) respectively

Conclusions: VIDAS D-dimer method is a sensitive method that can be used in the initial management of deep vein thrombosis if a level of 900ng/dl is used as a cut-off point for exclusion of deep vein thrombosis. VIDAS D-dimer method is not a specific test so it cannot be used for the diagnosis of deep vein thrombosis.

Key words: D-Dimer, Diagnosis, DVT

Introduction:

It has been accepted that an objective diagnosis of deep vein thrombosis is mandatory because clinical evaluation is inaccurate. This is unfortunately because clinical features can be used to classify patients with symptoms suggesting DVT and to improve diagnosis strategies.[1] Studies have demonstrated that by categorizing the patients' pretest probability of DVT into low, moderate, or high likelihood, diagnostic precision can be improved [2].

Investigators demonstrated that the use of model of pretest clinical probability of DVT combined with common femoral and popliteal vein compression ultrasound decreased the number of false-positive and negative diagnoses, using ascending venography as the definitive diagnostic test [3].

The clinical features in an extensive venous thrombosis are more reliable since majority of the patients usually present with severe pain in the calf, thigh, or rapid swelling of the leg. On examination the affected limb appear pale or cyanosed and often cold with poor capillary return. There is marked tenderness along the course of thrombosed vein in the calf muscle [4]. Femoral vein thrombosis is usually associated with swelling of the foot and calf but because the thrombi are rarely completely obstructive and the veins are paired, swelling is not universal. Ilio-femoral vein thrombosis represents the most extensive form of DVT and usually associated with tenderness in the groin and swelling of entire leg [5].

D-dimer has been extensively investigated during the recent years and has been consistently found to be of value in the diagnostic approach of venous thrombo embolism [6,7,8,9]. D-dimer is a neoantigen formed when thrombin initiates the transition of fibrinogen to fibrin and activates factor XIII to cross link the fibrin formed [10].

The D-dimer is a fragment of fibrin that contains one intermolecular cross-link between the gamma chains of two fibrin monomers. This cross-linkage occurs in fibrin but not fibrinogen. It is thus specific for fibrin. Fibrin D-dimer derivatives were not detected in either citrate or EDTA anticoagulated plasma from healthy persons [11].

A wide variety of diseases were associated with a positive Dimer test assay in hospitalized patients many of these diseases have been reported to be associated with an increase in fibrinolytic activity [11].

Increased levels of D-dimer (cross link fibrin fragment) have been found in patients with deep vein thrombosis, acute myocardial infarction, acute pulmonary embolism,

unstable angina, and disseminated intravascular coagulation [12,13,14].

Plasma from nearly 40% of pregnant women with pre-eclampsia was reported positive for D-dimer. Patients with D-dimer had more sever disease [15]. While the sensitivity of plasma D-dimer measured by ELISA in the diagnosis of DVT is high, the utility of ELISA methods is limited in a clinical setting [16].VIDAS D-dimer is an automated ELISA D-dimer test offering high analytical performance. The single -dose and ready-to-use test format allows VIDAS D-dimer to run individual tests without additional cost. More importantly results can be provided to clinicians in a very short time.

A lower usefulness of D-dimer in elderly patients with suspected venous thromboembolism due mainly to a lower specificity of this test in this subset of patients has been reported [17].

Venous Duplex Imaging often allows direct visualization of the thrombus. Thrombus may be difficult to be visualized in its acute form. The addition of color flow imaging facilitates the identification of non-occluding clots. Thrombus echogenicity increase with age of the clot [18].The presence of an echogenic band within the lumen of the vein has considered as representing of thrombus, however, this phenomenon can frequently be mimicked by turbulent flow condition. When the vein is compressed this artifact is eliminated if there is thrombus [19].

Patients and methods:

A total of 50 patients with clinically suspected DVT admitted to vascular department in Surgical Specialties Hospital/Medical City in Baghdad were included in this study during a period of 12 months (October 2012- October 2013). A fully detailed history and medical examination were performed. Patients with history of old DVT within the last year, patients on anticoagulant therapy, and patients with severe infectious or inflammatory conditions were excluded from the study.

Duplex Sonography: All patients underwent duplex scanning of the symptomatic limb or limbs by a vascular radiologist who was blinded to the results of D-dimer test. The pelvic and inguinal veins ,as well as both the deep and superficial femoral veins, were scanned with patient in supine position .The popliteal segment was scanned from a posterior position ,with the patient lying on the abdomen .The distal venous segment ,including the posterior tibial veins, the peroneal veins ,the gastrocnemius veins ,and the soleus veins ,were scanned with the patient in a sitting position .Duplex sonography was used as the gold standard in this study for diagnosis of DVT.

Sample Collection: 1.8 ml of venous blood was collected by a clean venipuncture from each patient in a collecting tube containing 0.2 ml of 3.2% sodium citrate and centrifuged at 4000 rpm for 15min within 4 hours after collection .Platelet poor plasma was collected and then frozen at –20° C for a maximum of one month for analysis .

D-dimer Assay: All samples were thawed and recentrifuged prior to analysis. Plasma D-dimer for all samples was assayed by a rapid method VIDAS D-dimer .Tow controls negative and positive have been run with each test .

Results:

The results presented in this chapter were based on the analysis of 50 patients with suspected DVT, in 37 (74%) of them DVT was confirmed (group1) and in 13 (26%) of them DVT was excluded (group 2) by venous duplex sonography (figure 1) .

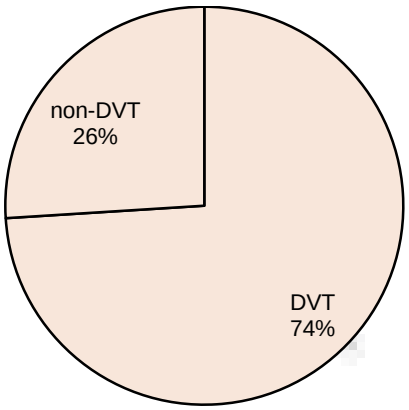

Figure (1): DVT and non DVT groups according to the result of venous

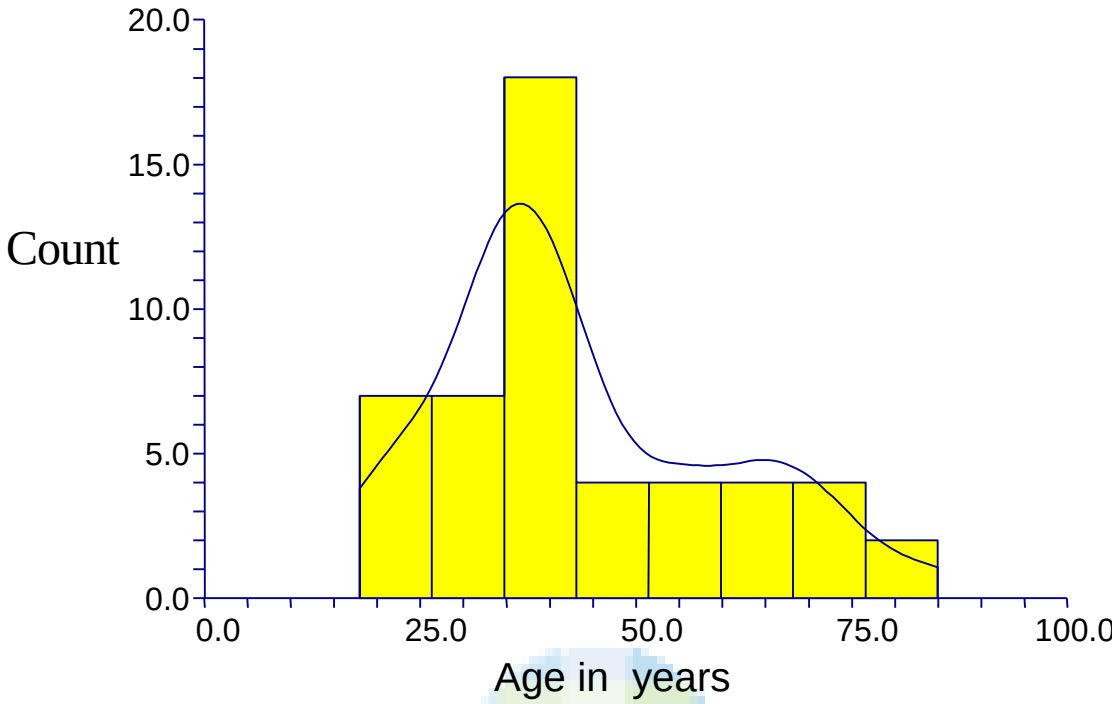

Figure (2): The age distribution of the patients with DVT.

The age of patients with DVT ranged between 18-85 year with a mean of 43 ± 4 years, and standard deviation of 16.64 and standard error 2.35, the majority of patients are between 25-50 years of age (figure 2).

Table (1) : The base line characteristics of DVT and non- DVT groups.

	DVT group	Non-DVT group
Age mean	43.4 years	45.2 years
Sex	Male 33 ,Female 5	Male 10 ,Female 2
Surgery or Trauma	15	2
Pregnancy	4	0
Malignancy	8	0
Varicosity	9	7
No risk factors	12	2

The above table shows associated risk factors of DVT: Male sex is significantly associated with DVT (P=0.0005). Surgery and trauma were significantly associated with DVT (P=0.0003). Malignancy risk group includes 5 patients with gastrointestinal tract, 2 patients with pulmonary carcinoma, and one patient with non-Hodgkin lymphoma, malignancy is significantly associated with DVT (P=0.0006). Four pregnant women of different stages of pregnancy, two of them are grand multigravida. Pregnancy is significantly associated with DVT (P=0.0005).only 14 patients of the total 50 patients do not have comorbid condition.

Table (2): D-dimer means, standard deviation, and range in DVT and non DVT groups

	D-dimer mean ±SD in mg/dl	*MIN in ng/dl*	*MAX in ng/dl*	*Range of D- dimer in ng/dl*
DVT	5498.021 ± 3266.133	2571.39	11000.350	8428.960
Non DVT	1906.384 ± 1533.898	375.O	2251.7	1976.7

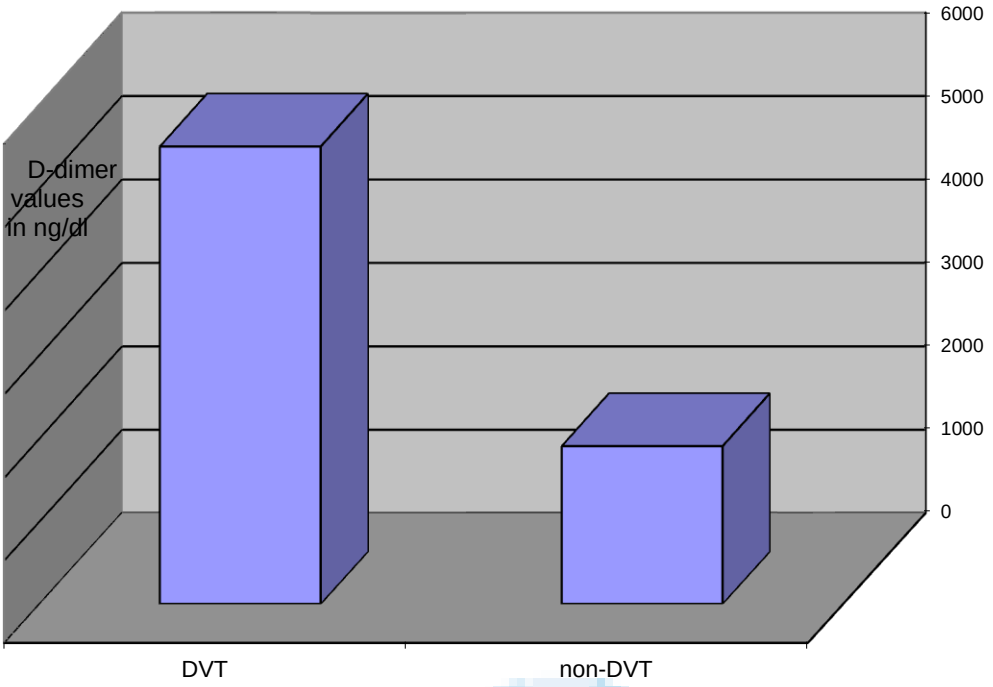

Figure (3) :the mean level of D –dimer

The table 2 and figure 3 show that the mean level was higher in DVT group (5498.02 ng/dl) compared to non DVT group (1906.38ng/dl) .The observed differences in mean D-dimer levels between the two groups was statistically significant (p=0,0003) .

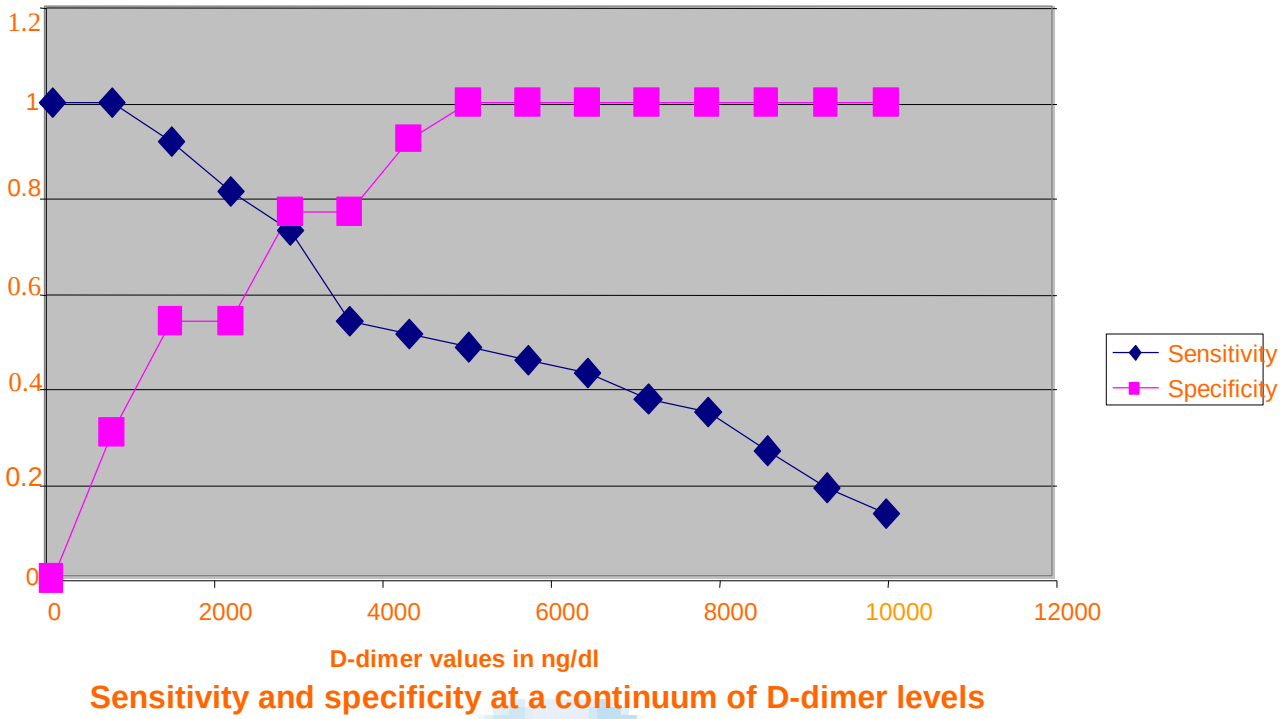

Figure (4) : The sensitivity and specificity of D-dimer test

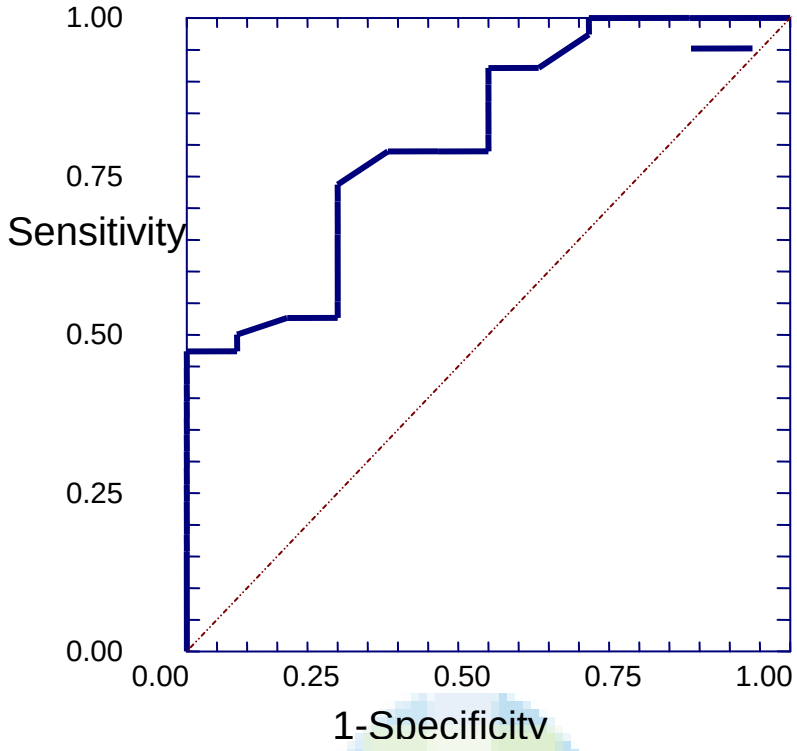

Figure (5): Receiver Operator Characteristic (ROC) curve plotting sensitivity and the false positive rate across continuum of D-dimer levels.

Figure (5) shows a ROC curve, plotting sensitivity and the false positive rate (1-specificity). Area under the curve is 0.81 with standard error of 0.06 indicate a relationship of D-dimer to the presence of DVT much greater than chance because D-dimer cut off values curve lying above the chance line.

Table (3): Sensitivity, specificity, positive, and negative predictive values at different cutoff points of VIDAS D-dimer.

Cut off Of D-Dimer	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
500	100%	33%	82%	100%
900	100%	33%	82%	100%
3000	71%	75%	90%	47%

Using sensitivity, specificity, negative and positive predictive values for specific D-dimer levels as cutoff points sensitivity and negative predictive values were maintained 100% up to the level of 900ng/dl ,while the specificity and positive predictive value were (33% ,82%) respectively .With increasing D-dimer levels the specificity and positive predictive value will increase while the sensitivity and negative predictive value decrease. At a cutoff point of 3000ng/dl the sensitivity and negative predictive value decrease to (71%, 47%) while the specificity and positive predictive value increase to (75% , 90%) respectively as shown in table(4)

Discussion:

Deep vein thrombosis has an annual incidence of 1/1000. An estimate of case fatality rate range from 1% - 5% , however , the incidence and the case fatality are very age dependent [(20)] .Early diagnosis of DVT and the prevention of its complication ,pulmonary embolism ,is highly desirable .While clinical examination cannot relied upon in isolation to make a diagnosis of DVT, its combination with appropriate history taking can provide useful information[(21)].Duplex scanning ,the present gold standard for the diagnosis of DVT , is relatively time consuming and expensive .

A rapid test with high sensitivity and high negative predictive value ,allowing preselection of patients requiring further sonography investigation , could decrease the number of sonography performed and results in significant cost reduction .

This study use a rapid and quantitative method for individual sample assay which is automated VIDAS D-dimer test to rule out the diagnosis of DVT . It reveals that excellent sensitivity (100%) and negative predictive values (100%) were maintained up to a cut-off level of 900ng/ml a level below which DVT could be safely excluded from a patient. A relatively good specificity of 75% at a level of 3000 ng /dl was found, indicating that the majority of patients with DVT had a level above this value. But patients with levels between 900ng/ml and 3000ng/ml could not be safely excluded from having a DVT.

This study agrees with most of the published literature on D-dimer [12,13,22,23].

Four out of fifty patients included in the present study who had D-dimer level below 900ng/dl were found by venous duplex to have no DVT that is mean approximately one tenth (n=4) of patients could have avoided a venous imaging study if a level of 900 ng /dl or less had been used to exclude DVT , this would have translated into a significant cost saving ,another potential benefit is the rapid time of the assay ,results being available within 1 hour .

VIDAS D- dimer assay showed a significant difference between the mean levels of D- dimer of patients with and without DVT (P=0.0003) which agree with most studies[24,25] .

However, in DVT group of patients the finding of high level of D-dimer (>10.000ng/dl) in patients with associated conditions like cancer and recent surgery is interesting but expected since these conditions can independently elevate D-dimer results in absence of obvious thrombosis which makes the test non-specific . Exclusion of patients with risk factors from this study was difficult as it further reduces the sample size and limits the value of the study since only 12 patients (10%)do not have comorbid conditions that would potentially elevate D-dimer .

The mean age of the patients was 43 years and two patients were more than 70 years with D-dimer levels >500 ng/dl .In both the venous duplex results were negative for DVT and they do not have other condition which elevate D-dimer level this finding agrees with the study of (Carlos et al) [26] which suggests a higher cut-off value for elderly patients for exclusion of DVT since the baseline of D-dimer increases with age [17] .

Conclusion:

1. VIDAS D-dimer method is a sensitive method that can be used in the initial management of deep vein thrombosis if a level of 900ng/dl is used as a cut-off point for exclusion of deep vein thrombosis

2. VIDAS D-dimer method is not a specific test so it cannot be used for the diagnosis of deep vein thrombosis.

Recommendation:

It is recommended to use VIDAS D-dimer method in emergency unit as an initial management of DVT by rolling out the diagnosis of DVT in patients with negative result (<900ng/dl).

References:

1. Anthony J, and Kagan SA, "Venous disease" In: Sabstion Text book of surgery 16th edition, chapter 64: 1418-1443.

2. Scurr JH, "Venous disorder" Baily and Love's, Short Practice of Surgery, 22th edition. Chapman and Hall Publishing Co., 1995; 149-178.

3. Anthonie WA, Lensing MD, "Detection of deep vein thrombosis by real time B mode ultrasonography" N. Eng. J. Med., 1989; 320: 342.

4.Rodgers GM, "Thrombosis and antithrombotic therapy" In: Wintrobe's Clinical Hematology" (eds); Lee GR, Forerster J, Lukens J, Paraskevas F, Rodgers GM,.. 10th edition. Philadelphia. 1999: 684-764.

5.Green RM and Oureil K, "Venous and lymphatic disease" In: "Schwartz principle of surgery" 7th edition, 1999; 1005-1031.

6. G. Der Sahakian et al" Accuracy of D-Dimers to Rule Out Venous Thromboembolism Events across Age Categories" Emergency Medicine InternationalVolume 2010 (2010), Article ID 185453, 4 pages

7. Sartori M et al, "The Wells rule and D-dimer for the diagnosis of isolated distal deep vein thrombosis" J thromb hemost.2012 Nov;10(11):2264-9. doi: 10.1111/j.1538-7836.2012.04895.x..

8. Benilde Cosmi1 et al ," Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism "JANUARY 21, 2010;BLOOD:115(3)

9. Sally Roertsonl" Medical news life science &medicine Selective strategy for D-dimer testing in DVT" Published on January 16, 2013 at 9:15 AM ·

10. Bick RL, "Disseminated intravascular coagulation and related

syndrome" In: "Haematology, Clinical and Laboratory Practis" (ed); Bick RB, Mosby year book, Inc. Publishing Company, USA, 1993; 1463-1493.

11. Greenberg CG, Devine DVT, McCrae KM, "Measurment of plasma fibrin D-dimer levels with the use of a monoclonal antibody coupled to latex beads" Am. J. Clin. Pathology, 1987; 1: 94-100.

12. Krushkal Jb, Commer ford PJ, Aranks JJ, et al. "fibrin and fibrinogen related antigens in patients with stable and unstable coronary artery disease" N. England. J. Med., 1987; 317(22): 1361-1365.

13. Bounameaux H, Cirafici P, de Moerloose P, et al. "Measurment of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism" Lancet, 1991; 337(87764): 196-200.

14. Heaton DC, Billings JD, and Hickton CM, "Assessment of D-dimer assays for the diagnosis of deep vein thrombosis" J. Lab. Clin. Med., 1987; November:588-591.

15. Troffatter KF Jr, Howell ML, Greenberg CS, et al. "Use of the fibrin D-dimer in screening for coagulation abnormalities in pre-eclampsia" Obst. Gynecol., 1989; 73(3 part 1):435-440.

16. Brenner B, Pery M, Lanir N, et al. "Application of a beside whole blood D-dimer assay in the diagnosis of DVT" Blood-coagulation-fibrinolysis, 1995, may, 6(3): 219-22, (abstruct).

17. Kario K ,Matsuo T ,Kobayashi H ; " Which factors affect high D-dimer levels in the elderly ? " Thromb. Res. 1991 ; 62 : 501-508 .

18. Anthonie WA, Lensing MD, "Detection of deep vein thrombosis by real time B-mode ultrasonography" N. Eng. J. Med., 1989; 320: 342.

19. Scurr JH, "Venous disorder" Baily and Love's, Short Practice of Surgery, 22th edition. Chapman and Hall Publishing Co., 1995; 149-178.

20. Norstrom , "A prospective study of the incidance of deep vein thrombosis within a defined urban population ".J .Intern. Medicine , 1992 ; 232 : 155-16.

21. Wells PS ,Hirsh J, Andron DR et al., "Accuracy of clinical assessement of deep vein thrombosis " .Lancet , 1995 ; 345 : 1326 – 30 .

22.Van der Graaf F ,Van den Borne H . Van der Kolk M.,et al. "Examination of deep venous thrombosis with D-dimer test in comparison of 13 D-dimer methods in 99 outpatients suspectedof deep venous thrombosis using venography as reference standards " Thromb. Haemost. ; 2000,83:18-28.

23. Carter CJ , Doyle DL ,Dawson N ,et al. " Investigations into the clinical utility of latex D-dimer in the diagnosis of deep

venous thrombosis " Thromb. Haemost. 1993 ; 9 : 8-11.(abstruct)

24. De MOERLOOSE P. "Performances of the VIDAS D-dimer New assy for the Exclusion of venous Thromboembolism " Thromb.,Haemost. ,2001; 85:185–186.(abstruct)

25. Escoffre-Barbe M, Oger E,Leroyer C,et al . " Evaluation of a new rapid D-dimer assay for clinically suspected deep venous thrombosis (Liatest D-dimer) ".Am. J .Clin .Pathol. 1998; 109: 748-753.

26. Carlos A ,Angel M , Angela M ,et al. " Diagnosis of deep venous thrombosis in the elderly : A higher D-dimer cut-off value is better ? " Haematologica 2001; 86 :E28.

Correspondence to;

Dr.Lamyaa Jaafar Hammoodi Alqaisi

Senier Specialist in Hemopathology, Manager of Laborotry Department of Ibn Albitar Cardiac Specialized Center, Baghdad, Iraq.