Validation of New D-Dimer Cutoff Values to Increase its Diagnostic Utility as Biochemical Marker in Acute Venous Thromboembolic Disease

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ABSTRACT

Background: Diagnosis of venous thromboembolic disease (deep venous thrombosis and pulmonary embolism) is often inaccurate because signs and symptoms are nonspecific. Numerous clinical management trials using D-dimer which is one of the coagulation markers have shown that it has a sufficient specificity to assist in the diagnosis of venous thromboembolic disease.

Aim of the work: This study was done to validate the utility of D-dimer as a diagnostic biomarker for DVT using a higher cutoff values which may improve the test specificity.

Material and method: In this retrospective chart review study, we reviewed the hospital records of all patients for whom D-dimer assay was done in King Abdul Aziz Specialist Hospital, Al Taif - Saudi Arabia from January 2011 to October 2013. The study involved 141 individuals; 25 who were proved to be normal were chosen to serve as control group (Group I), 61 patients who were positive for DVT by duplex scanning (Group II) and 55 patients who had symptoms of DVT but showed negative results on duplex ultrasound(group III).

Results: The demographic data revealed statistically insignificant difference between all studied groups. No significant differences were detected between the studied groups, except for hemoglobin level which was significantly lower in patients of groups II and III than in control group. However, highly significant differences were detected between different studied groups as regards D-dimer. Analysis of the receiver operator characteristic (ROC) curve to establish the cutoff level of the studied marker in the diagnosis of DVT, verified that D-dimer value of 0.92 mg/L can accurately differentiate patients who were positive for DVT on duplex scanning from control group. Level of 2.81 mg/L for D-dimer was considered as a cutoff point that can differentiate patients who were duplex negative and free from thrombosis from those who eventually developed thrombosis.

Conclusion: This study suggests the importance of the use of modified D-dimer cut-off values that can safely differentiate patients who are free from venous thromboembolic disease from others who are positive for the disease sparing patients the unnecessary risks of anticoagulation. In addition it can detect the patients who will eventually develop thrombosis regardless their primary duplex ultrasound scanning results, so, they could receive anticoagulation treatment.

Keywords: D-Dimer, New Cutoff, Acute Venous Thromboembolic Disease, Taif

INTRODUCTION:

Deep venous thrombosis (DVT) and pulmonary embolism (PE) remain significant but preventable health care problems.[1, 2] In absence of specific clinical manifestations, diagnosis of venous thromboembolic (VTE) disease is often inaccurate and it is based mainly upon clinical suspicion in patients at risk.[1]Duplex ultrasound and other sophisticated imaging modalities remain essential for diagnosis, however, these procedures may not be readily available during off-hours making the availability of plasma markers for DVT more desirable.[3] The most widely used test, D-dimer, is a fibrin degradation product detected in the blood after a blood clot is degraded by fibrinolysis and is useful to exclude the diagnosis of DVT due to its high sensitivity but its specificity is much lower.[4]The low specificity of D-dimer for diagnosis of VTE, especially in elderly, in addition to the increased plasma D-dimer concentrations in patients with extensive inflammation, wound healing, malignancy, and patients with liver disease make D-dimer primarily valuable when used in conjunction with clinical prediction scores.[5, 6] Recent studies verified that, the application of age adjusted cutoff values for D-dimer tests substantially increases specificity without modifying sensitivity.[7] Other studies suggested that higher D-dimer cutoff values might increase its specificity improving its diagnostic accuracy and to reduce the use of venous duplex ultrasound scanning for ruling out DVT in their studied patients.[8-11]This study was done to validate the utility of D-dimer as a diagnostic biomarker for DVT using

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a higher cutoff values which may improve the test specificity.

Patients and method: In this retrospective chart review study, we reviewed the hospital records of all patients for whom D-dimer assay was done in King Abdul Aziz Specialist Hospital, Taif - Saudi Arabia from January 2011 to October 2013 after approval of the ethical committee. The study involved only the candidates who gave written consents to use the data in their hospital records. The study involved 141 individuals; 25 normal candidates, who were involved in other clinical trial and proved to be normal (with no clinical signs, symptoms or history of DVT) were chosen to serve as control group (Group I).Male to female ratio in group I was 1.3:1, their ages ranged from 20 - 62 years, with a mean of 42.8 ± 11.66 years.

Group II included 61 patients who were positive for DVT by duplex ultrasound. Their ages ranged from 28 - 65 years, with a mean of 44.04 ± 11.05 years with male to female ratio of 1.5:1. Patients of this group fulfilled the following inclusion criteria: their ages were 18 years or more, they had clinical manifestations suggestive of VTE and their diagnosis was confirmed to be a DVT by duplex ultrasound imaging.

Group III included 55 patients with symptoms of unilateral or bilateral leg pain or swelling but with negative duplex ultrasound for DVT. Their ages ranged from 28 - 70 years, with a mean of 44.56 ± 11.66 years and male to female ratio of1.08:1. The hospital records of all subjects were revised for clinical history with special emphasis on smoking, obesity, medications, especially oral contraceptive pills, personal or family history of DVT, concurrent medical problems, history of cancer, serious extremity injuries and history of recent surgery in addition to the data of the clinical findings suggestive of DVT or / and pulmonary embolism. Reports of duplex ultrasound examination of the affected extremity were revised for each patient. Concerning patients' laboratory data, the following results were emphasized; Complete blood count (CBC), prothrombin time (P.T), activated partial thromboplastin time (aPTT) and D-dimer levels.

Statistical Analysis: Results were expressed as mean ± standard deviation and the analyses were performed using SPSS version 15. Chi-Square test (X^2): was used for comparison of categorial data. Student's t-test: was used for comparison of numerical data. Diagnostic accuracy (DA): Cases correctly classified. A receiver operating characteristic (ROC) curve: used to illustrate the diagnostic properties of the test on a numerical scale. Sensitivity (true positive rate, false negative): How good the test is at detecting disease. Specificity (true negative rate, false positive): How good the test is at identifying normal. P value: < 0.05 was considered significant, ≤ 0.001 was considered highly significant, and ≥ 0.05 was considered insignificant.

RESULTS

The demographic, clinical, and hematological data revealed statistically insignificant difference between all studied groups except for hemoglobin level which was significantly lower in group II and group III patients when compared to control group (table 1 & 2). There was no statistically significant difference between group II and group III patients, as shown in table (3). D-Dimer results in the studied groups are shown in figure 1. There was a highly significant difference ($p = 0.001$) when we compared the D-dimer levels in group I and II (table 4). A highly significant difference ($p = 0.001$) was also found between controls (group I) and duplex negative patients (group III) as regards the biomarker levels (table 5). In comparing betweengroups II and III patients, a highly significant difference ($p = 0.001$was also verified (table 6). Receiver operator characteristic (ROC) curves (figures 2, A & B) were done to establish cutoff levels for the diagnosis of DVT, where a value of 0.92 mg/L of D-dimer that had 100% sensitivity, 100% specificity and 100% diagnostic accuracy was settled differentiating the control group (normal individuals) from the duplex positive group. Fifty five patients involved in this study (group III) were negative for DVT by duplex ultrasound; however, in a period of time ranging from 3 to 7 days, fifteen patients eventually developed positive criteria for DVT on scanning. Comparing patients who were negative for DVT by duplex ultrasound and did not develop thrombosis with patients of the same group who eventually developed thrombosis, Level of 2.81 mg/L for D-dimer was considered as a cut-off point that can differentiate patients who were duplex negative and free from thrombosis from those who eventually developed thrombosis with 77% sensitivity, 94% specificity, and 84% diagnostic accuracy.

DISCUSSION:

The lack of subjective clinical symptoms and objective clinical signs for venous thromboembolism (VTE) makes the diagnosis complicated.[8]Currently, both imaging modalities and serology are utilized to establish the diagnosis of DVT, however, there is no single blood test exists alone to diagnose DVT and various plasma molecules are regarded as the biomarkers of DVT including D-dimer, P-selectin, Factor VIII, thrombin generation, inflammatory cytokines, microparticles, fibrin monomer, leukocyte count and so on.[9] The sensitivity of D-dimer testing determines its safety in ruling out DVT; but its specificity is poor because fibrin is produced in a wide variety of conditions, such as patients with prolonged hospitalization, cancer, pregnancy, inflammation, infection and necrosis, so the negative predictive value of D-dimer is high, meanwhile, its positive predictive value is low.[10, 11]In this chart review study, there was no significant correlation between the laboratory variables of the studied groups, except for hemoglobin level which was significantly lower in both groups II (patients who were positive for DVT by duplex scanning) and III (patients who had symptoms of DVT but showed negative results on duplex ultrasound) if compared to the control group. The results of the studies of Ay *et al*.[12] and Fullmer[13], were in accordance with our findings except for the hemoglobin where they reported no statistically significant difference in peak hemoglobin and hematocrit levels between patients with thrombosis and those without thrombosis.

The patient records in the present study revealed that D-dimer level was significantly higher in duplex positive patients (Group II) than both control group (group I) and duplex negative patients (Group III). In agreement with our results, Rectenwald & his colleagues [11], Tajanko *et al*. [14], and Goldin& his group [15], reported that D-dimer concentration was significantly higher in patient groups when compared to control group. The elevated levels of D-dimer in cases of DVT can be explained by the massive activation of the coagulation system leading to generation of fibrin which is cleaved by plasmin into high molecular weight fragments that are digested several times more by plasmin leading to the formation of D-dimer.[16]The diagnostic sensitivity and specificity of the different cutoff values for the D-dimer in the current study were done using receiver operator characteristic (ROC) curves.

It was found that D-dimer cut-off point at 0.92 mg/L, showed 100% sensitivity and 100% specificity. These values were selected to differentiate between control subjects and patients with DVT whose diagnosis was documented by duplex, so that patients who have levels below these selected values can be safely regarded as DVT free and not given anticoagulant treatment. The results obtained by Goldin*et al.*[15]came in accordance with the findings of the present study. They found that D-dimer level of 0.9 mg/L was effective in predicting the presence of VTE among 734 studied patients.

The studies of Di Nisio *et al.*[10]; Legnani & his coworkers [17] and Ramaciotti *et al.*[18] supported the results of the current study; they declared that D-dimer value of 0.5 mg/L is a highly sensitive level that can safely exclude acute DVT without imaging. According to these cutoff levels, patients can be safely regarded as DVT free and not given thrombolytic therapy, thus sparing patients the unnecessary anticoagulation. It has been estimated that anticoagulant therapy is associated with 4% of all adverse events and 10% of potential adverse events in hospitalized patients.[17]

The newly estimated cutoff point of D-dimer (2.81 mg/L) can be used to confirm the presence of DVT in patients who were negative for DVT by duplex ultrasound and did not develop thrombosis from patients of the same group who eventually developed thrombosis. Thus patients with D-dimer levels above this cutoff value could receive anticoagulation treatment even before confirming diagnosis by duplex ultrasound scanning or when it is unavailable. Similar results are obtained by Melina *et al.*[19] However, Yamaki and his colleagues [20], recorded that D-dimer values using latex agglutination based assay at a cutoff of 1 mg/L have a sensitivity of 97% and specificity of 63% for exclusion of DVT concluding that the use of this cutoff value, would reduce the use of venous duplex ultrasound scanning by 44% for ruling out DVT in their studied patients. The difference of cutoff values between the studies may be related to the methodology.

D-dimer assays that have been validated as tests for DVT vary in their sensitivity and specificity, partly because of differences in their accuracy and partly because of the cutoff

value they use to define normality, i.e., trade-off between sensitivity and specificity.[21] So, to reach an accepted diagnostic accuracy a new standardized cut-off value must be established for each test.[8-11] Moreover Schouten *et al*.[7], verified that, the application of age adjusted cut-off values for D-dimer tests substantially increases specificity without modifying sensitivity, thereby improving the clinical utility of D-dimer testing particularly in patients aged 50 or more.

CONCLUSION

This study suggests the importance of the use of modified D-dimer cut-off values that can safely differentiate patients who are free from venous thromboembolic disease from others who are positive for the disease sparing patients the unnecessary risks of anticoagulation. In addition it can detect the patients who will eventually develop thrombosis regardless their primary duplex ultrasound scanning results, so, they could receive anticoagulation treatment.

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Table 1: Comparison between group I and group II patients as regards demographic, clinical, and hematological parameters

Parameter	Group I n = 25 No. (%)	Group II n = 61 No. (%)	X^2/t	p value	Sig.
Mean age (years)	42.8 ± 11.6	44.04 ± 11.05	0.094	0.734	NS
Sex Male Female	 14 (56%) 11 (44%)	 37 (60.7%) 24 (39.3%)	0.085	0.771	NS
Obesity +ve -ve	 12 (48%) 13 (52%)	 28 (45.9%) 33 (54.1%)	0.515	0.896	NS
Smoking +ve -ve	 11 (44%) 14 (56%)	 34 (55.7%) 27 (44.3%)	0.514	0.628	NS
OCPs +ve -ve	 0 (0%) 25 (100%)	 5 (8.2%) 56 (91.8%)	0.057	1.000	NS
Previous surgery +ve -ve	 2 (8%) 23 (92%)	 11 (18%) 50 (82%)	0.737	1.000	NS
History of DVT +ve -ve	 0 (0%) 25 (100%)	 7 (11.5%) 54 (88.5%)	0.735	1.000	NS
WBC ($\times 10^9$/L) Mean ± SD	8.59±3.58	9.86±5.85	0.166	0.877	NS
Hb (g/dL) Mean ± SD	11.86±2.23	10.39±2.45	2.222	0.031	**S**
Platelets($\times 10^9$/L) Mean ± SD	231.4±109.8	238±114.7	0.757	0.449	NS
PT (sec) Mean ± SD	14.6 ± 2.1	17.5 ± 4.5	0.039	0.969	NS
INR Mean ± SD	1.2 ± 0.2	1.4 ± 0.45	0.069	0.945	NS
aPTT (sec) Mean ± SD	35.7 ± 4.1	38 ± 7	1.212	0.226	NS

NS: non-significant; S: significant; HS: highly significant

Table 2: Comparison between group I and group III patients as regards demographic, clinical, and hematological parameters

Parameter	Group I n = 25 No. (%)	Group III n = 55 No. (%)	X^2/t	P value	Sig.
Mean age (years)	42.8 ± 11.6	44.56 ± 11.66	0.533	0.763	NS
Sex Male Female	 14 (56%) 11 (44%)	 28 (50.9%) 27 (49.1%)	0.843	0.532	NS
Obesity +ve -ve	 12 (48%) 13 (52%)	 24 (43.6%) 31 (56.4%)	0.405	1.000	NS
Smoking +ve -ve	 11 (44%) 14 (56%)	 25 (45.5%) 30(54.5%)	0.403	1.000	NS
OCPs +ve -ve	 0 (0%) 25 (100%)	 2 (3.6%) 53 (96.4%)	0.289	0.552	NS
Surgery +ve -ve	 2 (8%) 23 (92%)	 8 (14.5%) 47 (85.5%)	0.679	0.280	NS
History of DVT +ve -ve	 0 (0%) 25 (100%)	 4 (7.3%) 51 (92.7%)	0.687	0.219	NS
Age (years) Mean ± SD	42.8±11.6	44.56±11.66	0.629	0.530	NS
WBC ($\times 10^9$/L) Mean ± SD	8.59±3.58	7.58±3.75	0.898	0.374	NS
Hb (g/dL) Mean ± SD	11.86±2.23	10.24±2.23	2.352	0.024	**S**
Platelets($\times 10^9$/L) Mean ± SD	231.4±109.8	196.1±77.2	0.752	0.452	NS
PT (sec) Mean ± SD	14.6 ± 2.1	15 ± 1.5	1.053	0.292	NS
INR Mean ± SD	1.2 ± 0.2	1.25 ± 0.25	0.612	0.541	NS
aPTT (sec) Mean ± SD	35.7 ± 4.1	41 ± 10	0.725	0.395	NS

Table 3: Comparison between group II and group III patients as regards demographic, clinical, and hematological parameters

Parameter	Group II n = 25 No. (%)	Group III n = 25 No. (%)	X^2/t	P value	Sig

Mean age (years)	44.04 ±11.05	44.56 ±11.66	0.641	0.741	NS
Sex Male Female	 37 (60.7%) 24 (39.3%)	 28 (50.9%) 27 (49.1%)	0.515	0.628	NS
Obesity +ve -ve	 28 (45.9%) 33 (54.1%)	 24 (43.6%) 31 (56.4%)	0.096	1.000	NS
Smoking +ve -ve	 34 (55.7%) 27 (44.3%)	 25 (45.5%) 30(54.5%)	0.510	0.624	NS
OCPs +ve -ve	 5 (8.2%) 56 (91.8%)	 2 (3.6%) 53 (96.4%)	0.096	1.000	NS
Previous surgery +ve -ve	 11 (18%) 50 (82%)	 8 (14.5%) 47 (85.5%)	0.737	1.000	NS
History of DVT +ve -ve	 7 (11.5%) 54 (88.5%)	 4 (7.3%) 51 (92.7%)	0.857	0.355	NS
WBC($\times10^9$/L) Mean ± SD	9.86±5.85	7.58±3.75	1.096	0.273	NS
Hb (g/dL) Mean ± SD	10.39±2.45	10.24±2.23	0.202	0.841	NS
Platelets($\times10^9$/L) Mean ± SD	238±114.7	196.1±77.2	1.280	0.200	NS
PT (sec) Mean ± SD	17.5 ± 4.5	15 ± 1.5	0.347	0.556	NS
INR Mean ± SD	1.4 ± 0.45	1.25 ± 0.25	0.321	0.571	NS
aPTT (sec) Mean ± SD	38 ± 7	41 ± 10	0.333	0.564	NS

Table 4: Comparison between group I and group II patients as regards D-dimer levels

Parameter	Group I	Group II	X^2/t	P-value	Sig.
D-dimer (mg/L)	0.36±0.16	4.41±2.07	9.745	0.000	**HS**

Table 5: Comparison between group I and group III patients as regards D-dimer levels

Parameter	Group I	Group III	X^2/t	P value	Sig.
D-dimer (mg/L)	0.36±0.16	2.1±1.37	6.299	0.001	**HS**

Table 6: Comparison between group II and group III patients as regards D-dimer levels

Parameter	Group II	Group III	X^2/t	P value	Sig.
D-dimer (mg/L)	4.41±2.07	2.1±1.37	4.648	0.001	**HS**

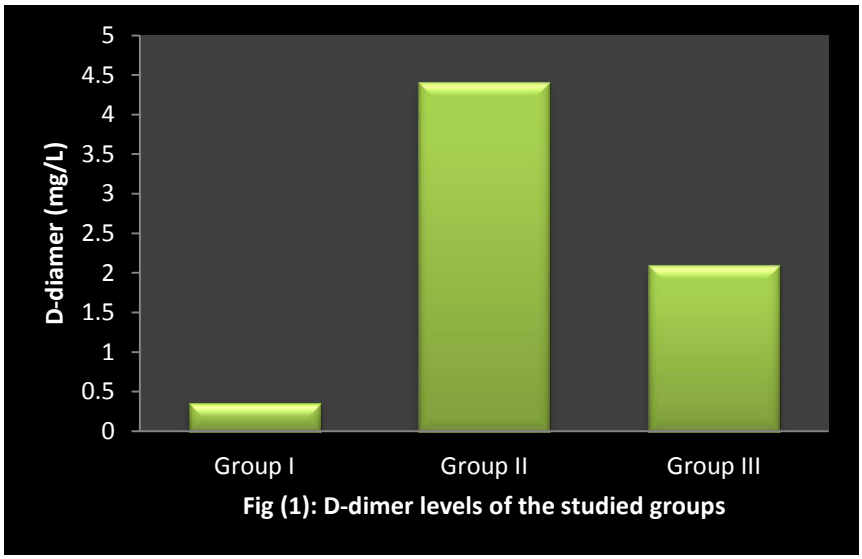

Figure 1: D-Dimer results (mean) in the studied groups

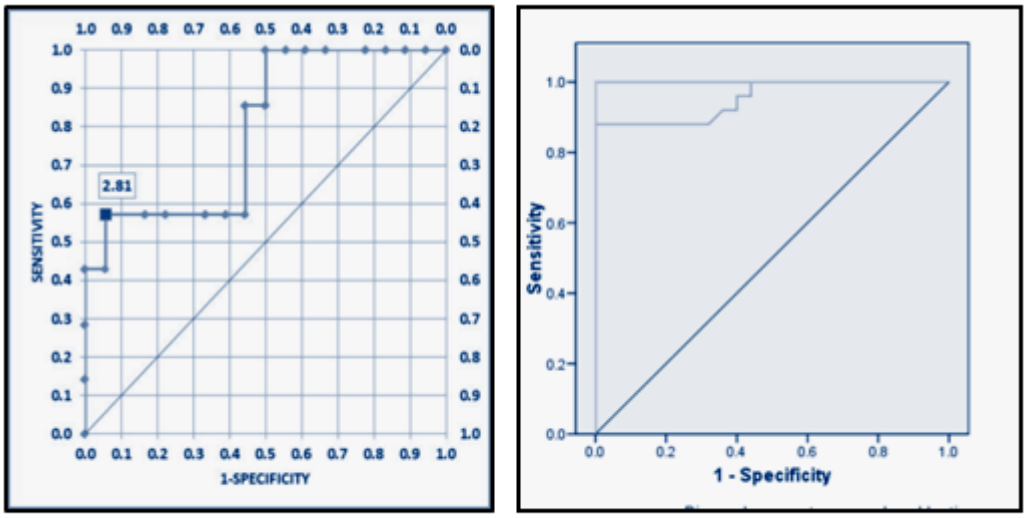

Figure 2: ROC curves; **A** showing the best cut-off values to differentiate control group and duplex positive group, **B** showing the best cut-off values to differentiate duplex negative patients without future thrombosis from duplex negative group who eventually developed thrombosis.