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DIAGNOSTIC UTILITY OF QUANTITATIVE D-DIMER TESTING IN CORRELATION WITH CT ANGIOGRAPHY IN RULING OUT THROMBOEMBOLISM- A PROSPECTIVE STUDY AT A TERTIARY CARE CENTRE

Pathology

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ABSTRACT

Background: Vascular Thromboembolism (VTE)- blockage of a blood vessel by the broken components of a blood clot, is commonly caused by Thromboembolism Deep venous thrombosis (DVT) and Pulmonary embolism (PE). It can also be caused by various other conditions, and have overlapping features. VTE's have significant morbidity and mortality, treatment carries significant side effects, hence, objective testing becomes must to establish or exclude the presence of thromboembolism. D-Dimer, a fibrin degradation product (FDP), appears in blood after degradation of blood clot by fibrinolysis. It is normally undetectable or detectable at a very low level, unless the body is forming and breaking down blood clots as in VTE. **Materials and Methods:** Quantitative D-Dimer test was performed using fully automated technique, on patient's serum. Latex particles coated with anti D-dimer monoclonal antibodies were mixed with the test plasma. In the presence of D-dimer, the latex particles agglutinate, the suspension clarifies and translates in low turbidimetric readings. All results were further correlated with their CT Angiography findings.**Results:** Most patients had D-Dimer value in range of 1.0 to 2.0 µg/ml. High (96.77%) Sensitivity shows that the test can be used safely to detect Thromboembolism even in early stages, whereas, High Negative Predictive value (93.54%), suggests safe exclusion in suspected cases. **Conclusion:** D-Dimer is highly sensitive, accurate and rapid test, but alone cannot conclude diagnosis. It is advisable to correlate with combination of Radiological investigations (CT Angiography) and clinical probability- Revised Geneva score and to establish a final diagnosis and plan an appropriate treatment.

KEYWORDS

D-dimer, CT Angiography, Deep Vein thrombosis, Pulmonary embolism

INTRODUCTION:

Thrombosis is the formation of a blood clot inside a blood vessel, causing obstruction of the blood flow. Injury to the vascular endothelium activates the coagulation pathway, forming blood clot (thrombus) composed of platelets and fibrin, hence preventing blood loss. A piece of either an arterial or a venous thrombus can get detached (embolus), which can travel through the circulation and lodge somewhere else as an embolism. This type of embolism is known as a thromboembolism. Complications can arise when a venous thromboembolism (VTE) lodges in the lung as a pulmonary embolism. Thrombosis is found to be the 3rd leading cause of cardiovascular death and leading cause of preventable deaths in hospitals.[1,2]

Venous thrombosis activates the coagulation and fibrinolytic systems, and results in elevated levels of fibrin spit products. Fibrin polymers are degraded by plasmin in the fibrinolytic process. One of the terminal products of fibrinolysis is the covalently linked D-Domain called the D-Dimer fibrin fragment[3]. D-Dimer antigen levels are elevated in the acute phase of clot formation as would occur in acute deep venous thrombosis, and also the fibrinolytic stage that would occur in the setting of acute pulmonary embolism. D-Dimers have a half-life of 4 to 6 hours. Continued fibrinolysis that occurs in DVT and pulmonary embolism causes the D-Dimer to remain elevated for about 7 days. Patients who present late in their course once clot organization and adherence begins, may have low levels of D-Dimers.[4]

D-Dimer levels correlate with the presence of fibrin clots without regard to location. It can remain elevated in a variety of other medical conditions such as trauma, recent surgery, haemorrhage, cancer, and sepsis that are associated with activation of the coagulation system and formation of fibrin clots. This explains the low specificity of the D-Dimer assay for only venous thromboembolism[5].

In recent years, many radiological techniques have shown significant advancements which help in confirmatory diagnosis of thromboembolic events. CT angiography uses a CT scanner to produce detailed images of both blood vessels and tissues in various parts of the body. During the exam, contrast material is injected through a small catheter placed in a vein of the arm. High-resolution CT images are captured while the contrast material flows through the blood vessels[6]. It has become the technique of choice for detection of pulmonary embolism due to its wide availability, short exam time, ability to see other diseases that may present like pulmonary embolisms, and a high degree of confidence in the validity of the test.[7,8]

AIMS AND OBJECTIVES:

1. To assess the diagnostic accuracy of Quantitative D-Dimer testing in suspected cases of thromboembolism.
2. To rule out Thrombo-embolism in suspected patients according to Revised Geneva scoring system.
3. Correlate Revised Geneva score and Radiological findings for thromboembolic events with D-dimer values.
4. To emphasise the need for invasive investigations like CT Angiography and other Radiological investigations in patients with low D-dimer values.
5. To calculate the Sensitivity and Specificity of Quantitative D-dimer testing in various thromboembolic events.

MATERIALS & METHODS:

The study was performed at a Tertiary care centre in Department of Pathology over a period of 2 years on 100 patients from Medicine, Surgery and Orthopaedics who were suspected of having venous thromboembolism, based on their presenting clinical presentation. All patients were evaluated according to the Revised Geneva scoring system. The **Geneva score** is a clinical decision rule used to estimate the pre-test probability of pulmonary embolism (PE) in patients in which this diagnosis was considered. The criteria were originally published by the clinical team of the Geneva University Hospital in 2001[9], and revised and simplified in 2006[10].

Quantitative D-Dimer tests were performed on the serum separated by centrifugation, from the whole blood sample. Tests were performed by fully automated technique using STAGO- Satellite Max machine. Latex particles coated with anti D-dimer monoclonal antibodies (MoAbs) were mixed with the test plasma. In the presence of D-dimer, the latex particles agglutinate and the suspension clarifies and

translates in low turbidimetric readings.

Interpretation for Quantitative Test:
Assay Range: 0.27 to 20 µg/ml FEU

Cut-off value: 0.5 µg/ml FEU

Positive D-Dimer: ≥0.5 µg/ml FEU

Negative D-Dimer: ≤0.5 µg/ml FEU

The D-Dimer results were correlated with the Radiological findings to confirm the diagnosis and plan the further management and treatment.

RESULTS:

Table no. 01: Age and Gender wise distribution of cases (n=100)

Age group	Male	Female	Total	Percentage
0 to 10 years	00	00	00	00.00%
11 to 20 years	01	01	02	2.00%
21 to 30 years	09	05	14	14.00%
31 to 40 years	13	03	16	16.00%
41 to 50 years	07	09	16	16.00%
51 to 60 years	20	09	29	29.00%
61 to 70 years	08	06	14	14.00%
71 to 80 years	06	01	07	7.00%
>80 years	00	02	02	2.00%
Total	64 (64%)	36 (36%)	100	100%

Table no. 01: Above table shows that, maximum number of cases were seen in age group of 51 to 60 years with male preponderance. Out of total 100 cases, 64% were male and 36% were female with M:F ratio of 1.8:1. Hence showing an overall high incidence in male population.

Table no. 02: High risk age group according to Gender (n=100)

Age group	Male	Female	Total / Percentage
<65 years	54/64 (84.37%)	32/36 (88.88%)	86 (86%)
>65 years	10/64 (15.62%)	04/36 (11.12%)	14 (14%)
Total	64	36	100

Table no. 02: According to Revised Geneva score[133.134], Patients belonging in age group of >65 years are considered as high-risk age group (Score 1). In present study, total 14 patients out of 100 were observed to be in this high-risk age group. Out of these 14, 10 were male and 04 were females, hence showing a male preponderance.

Table no. 03: Distribution of patients according to Risk Factors considering Revised Geneva score[9,10] (n=100)

Sr. No	Variable		Points	Male	Female	Total	Percentage
01	Risk Factors	Age >65 years	1	10	04	14	10.94%
02		Previous DVT/PE	3	05	04	09	7.03%
03		Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	2	20	06	26	20.31%
04		Active malignant condition (solid or hematologic malignant condition, currently active or considered cured <1 year)	2	00	00	00	00
05	Symptoms	Unilateral lower limb pain	3	09	08	17	13.28%
06		Hemoptysis	2	06	04	10	7.82%
07	Clinical signs	Heart rate 75-94 beats/min	3	09	14	23	17.96%
08		Heart rate >95 beats/min	5	10	04	14	10.94%
09		Pain on lower-limb deep venous palpation and unilateral edema	4	08	07	15	11.72%
		Total					100%

Table no. 03: Many patients presented with more than 1 risk factor/Symptoms/clinical signs. In such cases, each risk factor was counted separately and then a combined score was given to each patient to categorize him/her into Low/Intermediate/High risk category according to Revised Geneva Scoring system.

Table no. 04: Distribution according to Revised Geneva score based on Risk factors/Symptoms/Clinical signs. (n=100)

Sr.No	Risk score	Male	Female	Total	Percentage
01	Low risk (0 to 3)	43	19	62	62%
02	Intermediate risk (4 to 10)	19	17	36	36%
03	High Risk (≥11)	02	00	02	2%
04	Total	64	36	100	100%

Table no.04: Maximum number of patients belonged to low-risk category and male preponderance was observed.

Table no. 05: Distribution of cases according to Quantitative D-dimer values (n=100)

Sr. no	Range of value (µg/ml)	Male	Female	Total	Percentage
01	0.27 to 0.30	08	03	11	11%
02	0.31 to 0.40	08	04	12	12%
03	0.41 to 0.50	07	02	09	9.0%
04	0.51 to 0.60	01	05	06	6.0%
05	0.61 to 0.70	04	02	06	6.0%
06	0.71 to 0.80	02	01	03	3.0%
07	0.81 to 0.90	02	01	03	3.0%
08	0.91 to 1.0	03	00	03	3.0%
09	1.01 to 2.00	12	06	18	18%
10	2.01 to 3.00	06	05	11	11%
11	3.01 to 4.00	05	05	10	10%
12	>4.00	06	02	08	8.0%
	Total	64	36	100	100%

Table no 05: Maximum number of cases (20 cases) with a positive test result showed d-dimer value in the range of 1.01 to 2.00 µg/ml. In 32 cases d-dimer with value of <0.5 µg/ml (cut-off value for positive test result) was detected by Quantitative method. This indicates that the test has a high detection rate even at lower levels hence having a high sensitivity.

Table no. 06: Classification of cases according to risk category and D-dimer values (n=100)

Sr no	Risk category	D-dimer value	Male	Female	Total
01.	Low risk (0 to 3)	<0.5	19	08	27
		0.5 – 1.0	09	05	14
		1.01 -2.0	09	03	12
		2.01 – 3.0	03	02	05
		3.01 – 4.0	02	02	04
		>4.0	01	00	01
02.	Intermediate risk (4 to 10)	<0.5	03	01	04
		0.5 – 1.0	03	03	06
		1.01 -2.0	04	04	08
		2.01 – 3.0	03	03	06
		3.01 – 4.0	03	03	06
		>4.0	03	02	05
03.	High risk (>11)	<0.5	00	00	00
		0.5 – 1.0	00	00	00
		1.01 -2.0	00	00	00
		2.01 – 3.0	00	00	00
		3.01 – 4.0	00	00	00
		>4.0	02	00	02
	Total		64	36	100

Table no. 06: The present study shows maximum of 63 cases in low risk category with a male preponderance. In this category, maximum patients (27/100) showed a negative test with values lower than the cut-off range of <0.5 µg/ml. Range of D-dimer with a positive test result having maximum number of cases (14/100) was 0.5 – 1.0 µg/ml, followed by 1.01 to 2.0 µg/ml (12/100 cases). In low risk category, only 1 patient had a value of >4 µg/ml. Hence showing a high sensitivity with high detection rate even at lower values especially in patients with low risk criteria.

Patients with Intermediate risk were 35 out of 100. In this category, maximum number of patients (08/100) had values in the range of 1.01 to 2.0 µg/ml, followed by D-dimer value ranging between 2.01 to 4.0 µg/ml (total 12 cases out of 100). 6 Patients also had a lower D-dimer value in the range of 0.5 to 1.0 µg/ml. In this category, 5/100 patients showed a D-dimer value of > 4 µg/ml. Patients in the High-risk category had D-dimer values more than the detectable rate, with a range of >4 µg/ml. This shows that the high D-dimer values correlates with the high-risk criteria.

Table no. 07: Distribution of cases according to type of Investigation performed (n=100)

Sr. no	Investigation	Male	Female	Total	Percentage
01	CXR only	24	11	35	35.0 %
02	Doppler only	19	14	33	33.0 %
03	CT Angiography only	10	04	14	14.0 %
04	CECT only	04	00	04	4.0 %
05	MRI only	01	00	01	1.0 %
06	CXR+ Doppler	02	01	03	3.0 %
07	CXR+ CECT	03	04	07	7.0 %
08	CXR+ CT Angiography	00	02	02	2.0 %
09	Doppler + CECT	01	00	01	1.0 %
	Total	64	36	100	100%

Table no. 07: All the 100 patients included in the study were subjected to Radiological examinations depending on their presenting signs and symptoms. In 87 out of 100 patients, only a single investigation was performed. Chest X-Ray (CXR) was the most common single investigation performed followed by Doppler (to rule out associated Deep vein thrombosis in lower limb veins). In 14 cases, on CT-Angiography was performed and in 4 cases only Contrast Enhanced CT (CECT) was done for confirmation. In one patient MRI- Brain was performed which showed presence of micro thrombi.

In 13 patients, more than one radiological investigation was done to completely rule out or confirm thromboembolism. In such cases, the D-dimer value was either slightly elevated above the cut-off value of 0.5 µg/ml or it was below the cut-off value but patient showed high clinical suspicion of presence of Thromboembolism with an inconclusive CXR or Doppler. In these patients, a further invasive radiological procedure like CECT or CT-Angiography was performed.

Radiological Findings:

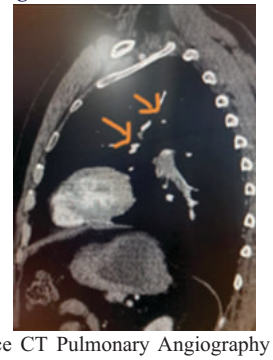

Image 01: 16 slice CT Pulmonary Angiography showing subtotal thrombosis of main pulmonary artery

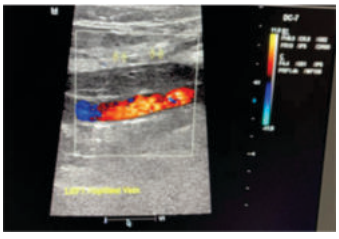

Image 02: Color Doppler scanning showing complete thrombosis of Popliteal vein

Table no. 08: Results of Quantitative D-Dimer tests (n=100)

Sr. No	Result	Male	Female	Total	Percentage
01	True Positive	37	23	60	60 %
02	True Negative	21	08	29	29 %
03	False Positive	05	04	09	9 %
04	False Negative	01	01	02	2 %
05	Total	64	36	100	100 %

True Positive cases (60/100): Test positive and disease- Venous thromboembolism (VTE)/ Pulmonary embolism (PE)/ Deep venous thrombosis (DVT) present.

True Negative cases (29/100): Test Negative and disease-VTE/PE/DVT absent.

False Positive cases (09/100): Test Positive but disease-VTE/PE/DVT absent

- On further investigations, thromboembolism was ruled out and conditions other than thromboembolism such as Rheumatoid Arthritis (3 cases), Diabetes Mellitus (2 cases), infective Bronchitis (1 case), Lung malignancy (1 case), Alcoholic liver disease (1 case), while one patient had history of polytrauma (1 case) but no evidence of thromboembolism was found on radiological examination.

False Negative cases (02/100): Test was Negative but further investigations confirmed Thromboembolism.

- Patients with D-Dimer value of ≥0.5 µg/ml are considered Positive. The D-Dimer value in these 2 cases were <0.5µg/ml but on further Radiological investigations like Doppler and Gold standard CT Angiography showed evidence of Thromboembolism related changes. Though negative, the values in these 2 cases were still near the cut-off range.

Table no. 09: Sensitivity, Specificity, Positive Predictive value, Negative Predictive value of Present study

Title	Sensitivity	Specificity	Positive predictive value	Negative Predictive value
Present study	96.77%	76.31%	86.95%	93.54%

- **Sensitivity** (TP/TP+FN) = 60/60+2 = **96.77%**
- **Specificity** (TN/TN+FP) = 29/29+9 = **76.31%**
- **Positive Predictive value** (TP/TP+FP): 60/60+9 = **86.95%**
- **Negative Predictive value** (TN/TN+FN): 29/29+2 = **93.54%**
- (TP-True Positive, TN- True Negative, FP- False Positive, FN-False Negative)

DISCUSSION:

Present study (2020) was carried out on total of 100 patients belonging to age group of 19 to 90 years. Maximum patients belonged to age group 51 to 60 years. Patients belonging to high risk category age group of >65 years according to Revised Geneva score were 18. In the study by Perrier Et al[11], patients belonged to wide age range of 17 to 95 yrs. The median age was 59 years for the group without PE (n=475) and 70 years for the group with PE (n=196). Study by Youssf Et al[12] involved patients of age range 25 to 70 years, with a mean age (49.1 ± 10.1) years. Study by Owaidah Et al[13], involved patients with age range 17–108 years with mean age at presentation being 52.64 years. In the study by Gomez Et al[14], the mean (standard deviation) age was 72 years. The age group of patients in all the studies is observed to be more or less similar, with maximum number of patients belonging to 5th to 6th decade of life.

Similar to the present study, male preponderance was seen in studies by Youssf Et al[12] (18 male, 12 female) and Sikora-Skrabaka Et al[15] with 189 male and 181 female. On the contrary, studies by Owaidah Et al[13] and Gomez Et al [14], showed a female preponderance with 73 (61.9%) women and 45 (38.1%) men in the former and 56 men (42%) and 76 women (58%) in the later.

In study by Owaidah Et al (2014)[13], the most common presenting symptom for suspected DVT was Swollen limb (51/118) and dyspnoea (42/118) for suspected PE. The most common presenting symptom in present study was palpitations (37/100).

In study by Perrier Et al[11], patients underwent clinical evaluation in the emergency center prior to undergoing any other test, and clinical probability of PE was rated between 0 and 100%. Lung scan, D-dimer assay, and lower-limb venous-compression ultrasonography were done on all patients, pulmonary angiography being done only in patients with an inconclusive non-invasive workup. Patients were not specified with low, moderate or high clinical probability for embolism.

Patients were subjected to more than one Radiological Test in the study conducted by Youssf Et al[12], this was however done in all cases included irrespective of the risk category. In the present study, Chest x ray was the most commonly performed radiological investigation, followed by Doppler. Invasive procedures like CT-Pulmonary Angiography and CECT were performed when the patients showed significant clinical sign/symptoms towards the presence of Thromboembolism but their D-dimer value was low to moderately raised above the cut-off value of 0.5µg/ml.

Perrier Et al[11], performed D-dimer using a cut-off of 500 mg/L which is similar to the present study. Pulmonary angiography was performed on

patients whose non-invasive workup was inconclusive. Youssf Et al[12] did not mention the value of D-dimer used as cut-off to make a diagnosis of thromboembolic events. Owaidah Et al[13] on the other hand used a cut-off value of <250µg/L, much lower to that of the present study by Quantitative method. Gomez Et al[14] in his study aimed to evaluate whether very high D-dimer values are specific to VTE. His results indicate that a D-dimer threshold >8000 ng/mL is not specific for the diagnosis of VTE. According to Sikora-Skrabaka Et al[15], the mean plasma D-dimer level in the group with confirmed PE (5,056 ng/mL) was significantly higher than in the group of patients without PE diagnosis (2,920 ng/mL). Hence reaching to a cut-off value of 2,152 ng/mL, which is approximately four times higher than the normal plasma D-dimer cut-off value.

All the studies discussed have tried to evaluate the diagnostic utility of D-Dimer in ruling out or diagnosing thromboembolism. Studies like Perrier Et al[11], Youssf Et al[12], Gomez Et al[14] and Sikora-Skrabaka Et al[15] gave more emphasis on Pulmonary embolism. Present study showed a high sensitivity (96.77%) and NPV (93.54%) which is in agreement with Perrier Et al[11] and Owaidah Et al[13]. Youssf Et al[12] too showed a high sensitivity of 90%. Sikora-Skrabaka Et al[15] too got a high sensitivity of 94.67%, very similar to present study which showed a sensitivity of 96.77% but shows a high variation in NPV. Present study showed the highest PPV (86.95%) which is in close comparison with that of Youssf Et al[12] with 80% of PPV. A wide variation is seen in specificity of all studies, with Owaidah Et al[13] having the lowest- 19%, followed by Sikora-Skrabaka Et al[15] (38.9%). Present study showed highest specificity of 76.31% in comparison to all other with lowest specificity shown by Sikora-Skrabaka Et al[15] (6.8%). Similarly, a wide variation was seen in the values of NPV when compared. Owaidah Et al[13] showed the highest NPV of 100%, followed by Perrier Et al[11] (99.5%) and Present study with NPV of 93.54%. Youssf Et al[12] showed the lowest NPV (60%) followed by Sikora-Skrabaka Et al[15](66.7%).

CONCLUSION:

- Thromboembolism is a very common, frequently occurring and potentially severe disease occurring in a wide age group of patients.
- It requires urgent diagnosis and treatment to avoid the related complications and high mortality.
- Clinical presentations of thromboembolism are very non-specific and require definitive confirmation by imaging studies.
- The decision for the type of Radiological investigation was based on the patient's clinical signs and symptoms and the consent to go for an invasive procedure.
- Our study observed a high concordance with the positive test result and positive radiological sign for the presence of thromboembolic event.
- Quantitative D-dimer has a high sensitivity and Negative Predictive value (more than 90%).
- It can be used as a reliable screening test in diagnosing or ruling out thromboembolic events even at a primary centre.
- Since D-Dimer levels are also raised in various other conditions like old age, pregnancy, chronic immobilization, obesity, surgery, malignancy etc., it was observed that, for an accurate diagnosis and treatment, it is advisable to combine the D-dimer findings with clinical probability (Revised Geneva score) and Radiological findings (CXR, Doppler and/or CTPA).
- This will aid the clinician in accurate diagnosis and treatment plan and avoid the need of invasive and expensive investigation procedures like CECT/CTPA.

Ethical Pproval:

Ethical approval of the parent Institute was taken prior to initiation of the study. Ref. No. IEC/Certi/ 01/01/2019 (M.P. Shah Govt. Medical College & Guru Gobindsingh Hospital, Jamnagar)

Conflict(s) Of Interest:

Authors have declared that no conflict(s) of interest exists.

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