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Study of D-dimer as a marker in risk stratification of patients with acute pulmonary embolism

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ABSTRACT: Background: Acute pulmonary embolism (PE) is a major health problem and an important cause of morbidity and mortality, despite advances in prophylaxis, diagnostic modalities and therapeutic options. Focus has recently shifted towards risk stratification of patients with PE as prognosis depends on the timely delivery of optimal therapeutic strategies.

Aim: This study was conducted with the aim to analyze the D-dimer level in risk stratification of PE patients by comparing with RV/LV ratio and in-hospital outcome.

Method: We performed a prospective observational study in which 50 consecutive acute pulmonary embolism patients diagnosed on computed tomography pulmonary angiography (CTPA) were taken and their D-dimer levels were compared with RV/LV ratio. All the patients were followed for clinical outcome (survived/ died) during their hospital stay, till discharge from the hospital.

Results: Out of 50 patients, 20 patients (40%) were having RV/LV ratio ≤1 while 30 patients (60%) having RV/LV ratio >1. D-dimer level showed statistically significant difference between RV/LV ratio groups (p-value 0.002) and outcome groups (alive/death) (p-value <0.001). Receiver operating characteristic curve (ROC curve) analysis of D-dimer showed that D-dimer levels can predict right ventricular dysfunction (RV/LV ratio>1) with area under curve(AUC) 0.7447 (p value <0.05). ROC curve analysis also showed that cut-off value of 14.4 µg/ml of D-dimer was able to predict in-hospital mortality with 100% sensitivity, 93.5% specificity and 94% accuracy.

Conclusion: Our study concluded that D-dimer level has clinical utility as a marker in the evaluation of the risk stratification of pulmonary embolism and it correlated well with the in-hospital outcome of the patients.

Keywords: Acute pulmonary embolism, D-dimer, Right ventricular dysfunction, Computed tomographic pulmonary angiography

I. INTRODUCTION

Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease after myocardial infarction and stroke.[1] It is a major health problem and an important cause of morbidity and mortality, despite advances in prophylaxis, diagnostic modalities and therapeutic options.[2,3] The incidence of PE is thought to be lower in Asia [4,5] but recent data suggest that the incidence and causes of PE may be similar between Chinese and Caucasian populations.[6] Risk factors includes advanced age, prolonged immobility, surgery, trauma, malignancy, pregnancy, estrogen therapy, congestive heart failure, and inherited or acquired defects in blood coagulation factors.[7] Among all causes for PE, deep venous thrombosis (DVT) is the most common.[8] PE and DVT are parts of the same process, venous thromboembolism. DVT can be found in about 70% of patients with PE.[9]

D-dimer is a fibrin degradation product generated from blood clot degradation by fibrinolysis.[10] Elevation of D-dimer indicates endogenous although often ineffective thrombolysis. The sensitivity pattern of D-dimer is >80% for DVT and >95% for PE.[7]

Computed tomographic pulmonary angiography (CTPA) has progressively been used as the preferred imaging modality for the diagnosis of pulmonary embolism.[4] Clinicians are concerned about PE, because of its high risk of mortality. If left untreated (most often because undiagnosed), acute PE has a lethality high as 59%, whereas adequately treated acute PE leads to death in only 7% of cases.[11]

Blood D-dimer levels can be used to assess the risk stratification of patients with acute

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PE, who are at risk for adverse clinical outcome.[12] The D-dimer has been increasingly used as a marker in the evaluation of the extent of the embolic disease. This study was conducted with the objective of comparing D-Dimer levels with RV/LV ratio on CTPA to assess severity and in-hospital outcome of the patient (alive/death) in PE patients.

II. MATERIAL AND METHOD

This study was a prospective observational study conducted in the Department of radiology, Apollo Hospitals, Bangalore, during the period of May 2013 to May 2014. The study was approved by Scientific and Ethical committee of the hospital. In this study, consecutive 50 patients (met inclusion criteria) were taken whose samples were evaluated for D-Dimer levels and had diagnosed to have acute pulmonary embolism on CTPA. For all the patients clinical data, including demographic and laboratory data were collected.

The STA-Liatest D-Di test kit was used in our hospital for quantitative assessment of D-dimer value. This test is based on immune-turbidimetric method. The D-dimer value ≥0.5 µg/ml was considered as positive test.

CTPA was done as per standard protocol followed in radiology department of the hospital. RV- to -LV (RV/LV) ratio was taken from CTPA at the level of maximum luminal axial diameter of ventricles.

Patients were divided into two groups on the basis of severity of acute PE; RV/LV ratio ≤1 and RV/LV ratio >1. Patients with RV/LV ratio >1 were considered as criteria for severity of acute pulmonary embolism. [13-15] Patients were followed during their hospital stay for recording short-term outcome as "alive" or "death".

Inclusion Criteria:

- All patients with confirmed acute pulmonary embolism on CT pulmonary angiography in the Apollo Hospitals, Bangalore, were included.
- Age: equal or above 18 years of age
- Gender: both male and female

Exclusion Criteria:

- Less than 18 years of age
- Pregnancy
- Renal derangement / impairment
- Chronic pulmonary thromboembolism
- Dilated cardiomyopathy
- Myocardial infarction

Statistical Analysis

Statistical analyses were performed by using software programs [SPSS software version 17.0, SPSS for Windows (Microsoft)], and Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA). Variables were expressed as mean ± SD and percentage. We used the chi-square test for comparisons of categorical variables and the student's t-test for comparisons in the distributions of continuous variables. Using receiver-operator characteristic (ROC) curves the area under the curve (AUC) of D-dimer for predicting right ventricular dysfunction (RVD) was compared. ROC curve were also compared for in-hospital mortality and optimal cut-off values, weighted for higher sensitivity, specificity and accuracy of the above parameter. For all tests, statistical tests used at 5% level of significance p-value <0.05 considered as significant.

III. RESULTS

The consecutive 50 patients with more than 18 years of age, who underwent D-Dimer test and diagnosed to have acute pulmonary embolism on CTPA were taken.

Age:

The mean age of the patients was 51.50 ± 15.45 years (mean ± SD). Majority of the patients in this study were in the age group of 51 - 60 years.(Table 1) So with increasing age, incidence of patients with PE was not increasing. Out of total 50 patients, there were 32 male and 18 female patients.

Table 1: Age group showing distribution of patients.

Age in years	No. of patients	%
≤30	6	12.0
31-40	7	14.0
41-50	10	20.0
51-60	14	28.0
61-70	8	16.0
>70	5	10.0
Total	**50**	**100.0**

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RV/LV ratio:

RV/LV ratio >1 was seen in 30 patients(60%) with mean age 49.80 ± 16.92 years (mean ± SD) and RV/LV ratio ≤1 was seen in 20 patients(40%) with mean age 54.05 ± 12.93 years (mean ± SD). There was no statistically significant difference in age distribution of patients in two RV/LV ratio groups (p-value = 0.346). (Table 2) It suggests 60% patients were having right ventricular dysfunction (RVD).

Table 2: Age groups showing distribution of patients in RV/LV ratio ≤1 and RV/LV ratio >1 group.

Age (years)	RV/LV ratio	
	≤1	>1
<30	0	6
30-40	4	3
41-50	4	6
51-60	6	8
61-70	4	4
>70	2	3
Total	20	30
Mean ±SD	54.05 ±12.93	49.80 ±16.92

D-dimer:

Out of 50 patients, maximum patients (60%) had D-dimer levels between 1.01 to 5.0 µg/ml. (Table 3) None of the patient had D-dimer level less than 0.5 µg/ml or more than 20 µg/ml.

Table 3: Showing distribution of patients according to the level of D-dimer.

D-dimer (µg/ml)	Pulmonary embolism (Number of cases)	%
0.51-1.0	2	4
1.01-5.0	30	60
5.1-10.0	7	14
10.1-15.0	5	10
15.1-20	6	12
Total	50	100

Table 4: Association of D-dimer levels with respect to RV/LV ratio.

	RV/LV ratio		Total (n=50)	P value
	≤1 (n=20)	>1 (n=30)		
• D-dimer(µg/ml) Mean ±SD	3.06±2.10	8.02±6.70	6.04±5.85	0.002**

D-dimer value showed statistically significant difference between RV/LV ratio groups with p-value 0.002. (Table 4)

ROC curves analysis for right ventricular dysfunction (RV/LV ratio>1)

ROC curve of D-dimer showed area under curve 0.7447 with p value <0.05. So D-dimer can predict right ventricular dysfunction (RV/LV ratio>1). (Table 5)

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Table 5: ROC curves of D-dimer for RVD (RV/LV ratio>1).

Variable(s)	AUC	P-Value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
D-Dimer	0.7447	<0.05	0.60766	0.88166

Outcome

Out of 50 patients, 4 patients died during their hospital stay while 46 patients were discharged alive, so 8% in-hospital mortality was noted in our study. (Table 6)

Table 6: Age distribution of patients with outcome.

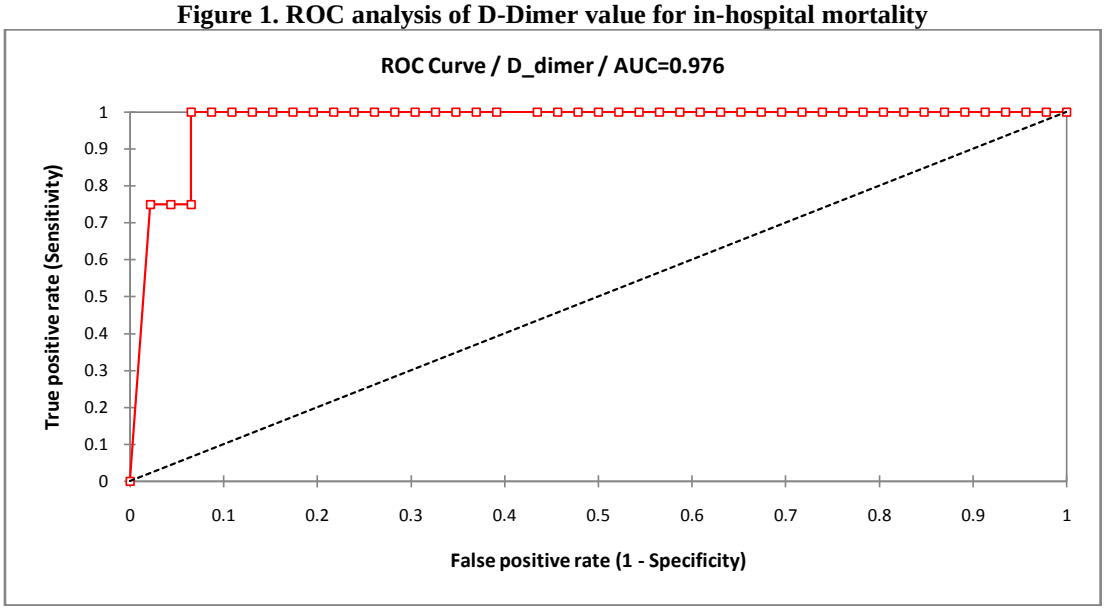
Age in years	Outcome		Total
	Alive	Death	
≤30	5	1	6
31-40	6	1	7
41-50	10	0	10
51-60	13	1	14
61-70	8	0	8
>70	4	1	5
Total	**46**	**4**	**50**

Table 7: Association of D-dimer levels with respect to outcome.

	Outcome		Total (n=50)	P value
	Alive (n=46)	Death (n=4)		
• D-dimer(µg/ml) Mean ±SD	4.94±4.64	18.64±2.73	6.04±5.85	<0.001

D-dimer value showed statistically significant difference between outcome groups (alive/death) with p-value <0.001. (Table 7)

Figure 1. ROC analysis of D-Dimer value for in-hospital mortality



Receiver operating characteristic curve (ROC curve) analysis showed that cut-off value of 14.4 µg/ml of D-dimer was able to predict in-hospital mortality with 100 % sensitivity, 93.5% specificity and 94% accuracy. (Figure 1)

IV. DISCUSSION

This study included 50 consecutive patients, who were diagnosed to have acute PE on CTPA and analyzed their D-dimer levels. RV/LV ratio >1 was specifically chosen in this study as it is the cut-off that has been most commonly used to define RV dysfuction in the literature.[5]

In our study, the mean age of the patients was 51.50 ± 15.45 years (mean ± SD), which was lesser than other previous studies.[16,17] Majority of the patients in this study were in the age group of 51-60 years. There was no significant increase in incidence of acute PE noted with increasing age in our study. This finding contradicted the findings with earlier studies, which showed that the incidence of PE increases with advancing age.[18-20] The reason for this discrepancy in age may be because of different geographical location.

Out of 50 patients, 20 patients (40%) were having RV/LV ratio ≤1 while 30 patients (60%) having RV/LV ratio >1 in our study. It suggested that 60% patients were having RVD. There was no statistically significant difference in age distribution of patients in two RV/LV ratio groups (p-value = 0.346) indicating no significant contribution of age in right ventricular dysfunction.

In our study, we had assessed the D-dimer values for risk stratification in CTPA diagnosed PE patients. Risk stratification is currently recommended for the initial management of patients with acute pulmonary embolism.[21] D-dimer value showed statistically significant difference between both RV/LV ratio groups (RV/LV ratio ≤1 & RV/LV ratio >1) and outcome groups (alive & death). Ghanima et al also found significant association between log D-dimer, and between log RV/LV ratio after adjusting for age, gender and for the duration of symptoms.[22]

D-dimer levels correlate with the extent of PE on CTPA, but the use of D-dimer alone for the screening and diagnosis of PE is still controversial.[23,24] In our study, we found 2(4%) patients having D-dimer levels ≤1.0 µg/ml. However, none of the patient had normal D-dimer values (i.e., ≤0.5 µg/ml) and D-dimer elevations were seen in all the PE patients suggest high sensitivity. Gao et al[10] found four patients with D-dimer levels ≤1.3 µg/ml and 28 patients whose D-dimer levels were >1.3 µg/m among 32 patients. Other studies also showed high sensitivity but low specificity of D-dimer values in relation to PE. [25,26]

In our study cut-off values of D-dimer was found to be 14.4 µg/ml (100% sensitivity, 93.5% specificity and accuracy 94%), for predicting in-hospital mortality. Blamoun et al reported a cut-off level to distinguish mild/moderate from severe/very severe PE at a concentration of 12.35µg/mL, and found that this threshold selected a higher inpatient mortality and higher 60-week recurrence.[27] We did not follow up our patients after discharge. However, 4 patients died during their hospital stay while 46 patients were discharged alive so 8% in-hospital mortality was noted in our study. Ghaye et al showed 14.6% in-hospital mortality which was higher than mortality in our study.[16] The reason behind so much difference may be because of different study population. Becattini et al also concluded in their study that in patients with acute PE elevated D-dimer is associated with increased short-term and 3-month mortality, suggesting the potential of using this test for both diagnosis and risk stratification.[21] Lobo et al also suggested that D-dimer testing (using IL test) may help identify those patients with acute PE that should be treated in hospital. [28]

There are potential limitations of our study that could be addressed in future research. First the sample size was small and second the study was limited to the patients presented to our hospital. Therefore the results may not be generalized to other tertiary centres.

V. CONCLUSION

Our study concluded that D-dimer has clinical utility as a marker in the evaluation of the severity of PE and are positively correlated with right ventricle dysfunction on CTPA and short term outcome of the patient during hospital stay.

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