COMPARISON OF 128-SLICE SPIRAL COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY (CTPA) FINDINGS WITH PLASMA D-DIMER LEVELS IN PATIENTS WITH CLINICAL SUSPICION OF PULMONARY EMBOLISM

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ABSTRACT

Objective: To compare the effectiveness of plasma D-dimer levels with findings of 128-slice spiral computed tomography pulmonary angiography (CTPA) in patients with clinical suspicion of pulmonary embolism.
Study Design: Retrospective observational study
Place and Duration of Study: Department of Computed Tomography, Armed Forces Institute of Radiology & Imaging, Pak Emirates Military Hospital Rawalpindi, from Jan 2018 to Dec 2018.
Methodology: A total of 59 patients were inducted who presented in Emergency Department, Pak Emirates Military Hospital Rawalpindi with clinical suspicion of Pulmonary Embolism. The main symptoms were shortness of breath and chest pain. Plasma D-dimer levels of all patients were sent to laboratory and CTPA was performed at Computed Tomography department, Armed Forces Institute of Radiology & Imaging using 128-slice spiral computed tomography.
Results: 36 patients (61%) were males and 23 (39%) were females with an average age of 48.03 ± 18.06 years (range 23-85 years). Out of 59 patients, D-dimer levels were raised in 28 cases (47.4%) while 31 patients (52.6%) showed normal levels. Pulmonary Embolism was detected by CTPA in 30 cases (50.8%) while 29 patients (49.2%) were without obvious abnormality.
Conclusion: Plasma D-Dimer levels show low sensitivity, specificity and negative predictive value and cannot exclude Pulmonary Embolism without CTPA. Computed Tomography Pulmonary Angiography (CTPA) remains diagnostic modality of choice for definitive assessment of Pulmonary Embolism in patients reporting at the emergency reception.

Keywords: Computed tomography pulmonary angiography (CTPA), 128-slice spiral computed tomography, D-Dimer, Pulmonary embolism.

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INTRODUCTION

Pulmonary embolism (PE) is a disorder due to occlusion of a pulmonary artery or one of its branches by emboli from right heart/venous system leading to impairment of the respiratory system and pulmonary circulation.[1] Pulmonary embolism has an incidence of about 100-200 cases per 100,000.[2] It has a high mortality with mortality around 4% in 30 days and 13% mortality in 90-days.[3] Majority of cases of PE that eventually become fatal are not suspected on clinical assessment and hence remain without specific treatment.[4] PE remains the third most common cause of acute cardiovascular disease, with the first two being myocardial infarction and stroke. It remains an under diagnosed and fatal condition. Hence, a timely diagnosis is lifesaving.

Validated diagnostic algorithms exist today for evaluation of suspected PE but diagnostic algorithms are often not used correctly or only benefit the subgroups of patients.[5] British Thoracic Society (BTS) guidelines for the management of PE,[6] demonstrate the utilization of clinical probability assessment and D-dimer assays so that relevant radiological imaging can be put to use.[7] Computed tomography pulmonary angiography (CTPA), is the imaging modality of choice for diagnosis of patients with suspected PE.[8]

D-dimers are fragments of protein released into the circulation when a blood clot breaks down. Few studies suggest that D-dimer assay could be utilized on their own for identifying PE and reduced need for excessive CTPA scans.[9] However, estimates of sensitivity of D dimers for detection of PE range from 80-100%, and estimates of specificity from 23-63%.[10] The diagnostic value of D dimer remains questionable mostly because of the lack of optimal diagnostic threshold and confounding factors leading to elevated D-dimer levels.

In Pakistan, limited work has been conducted to compare the diagnostic value of D dimers and

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CTPA for diagnosis of PE. The aim of this study was to compare diagnostic value of D-dimer assay with findings of spiral computed tomography pulmonary angiography (CTPA), in the diagnosis of PE.

METHODOLOGY

It was a retrospective observational study conducted from January to December 2018. Fifty-nine consecutive cases with the suspicion of PE were evaluated using universal sampling method. The study was approved by the Ethical review board committee, AFIRI (IERB approval certificate no: 002).

Inclusion Criteria: Patients with suspicion of pulmonary embolism based on clinical findings of chest pain and dyspnea who had undergone plasma D-dimer levels were included in the study.

Exclusion Criteria: Patients with previous or chronic history of PE and patients who had not undergone plasma D-dimer levels were excluded from the study. Patients suffering contrast reaction were also excluded from the study.

D dimer levels were measured using semi quantitative method with manual dilutions in four glass tubes at Armed Forces Institute of Pathology (AFIP), Rawalpindi. Before use, the reagents were equilibrated to room temperature (20-25°C). 20uL D dimer latex reagent (0.83% suspension of latex particles coated with murine anti D-dimer monoclonal antibody, 10 mg/ml BSA and 0.1% Sodium azide) was used and poured into each tube with 20uL patient's plasma in tube 1.20ul patient's plasma in 1:2, 1:4 and 1:8 dilutions with dilution buffer was added for interpretation in tubes 2, 3 and 4 respectively. This was followed by pouring of drops from each tube on tile, mixing with 20uL reagent again, and observing for agglutination after 3 minutes under a strong light source. A positive result, indicating active fibrinolysis, was labelled when levels were at or greater than approximately 0.25 mg/ml (250 ng/ml). All CTPA scans were done using 128-detector CT equipment (Siemens 128 slice Somatom Definition AS, Germany) and intravenous contrast material was administered by CT automated injector.

In preparation for CTPA evaluation, intravenous access was obtained in each patient using an 18–20 G catheter through one of the veins in the forearm. Later on, 35 mL of non-ionic contrast material (Omnipaque) was given at a rate of 4.5 mL/sec by an automated injector. Initially a bolus dose of 10ml contrast material followed by 35ml of normal saline solution was given to visualize the main pulmonary trunk and calculate time delay to obtain adequate images. This was followed by remaining contrast dose of 25ml and 35ml of normal saline solution after 1 minute. Following a 10-second delay post injection of contrast, sections were taken.

During the procedure, patients were asked to hold breath. Scanning was done with patient in the supine position, with the arm of injection by their side and the other hand at level of the head. Scanning was done from lung apices till the diaphragm with slice thickness between 0.50-1.00 mm. Variable dose parameters automated by the CT scan machine itself were used according to weight of patient (CT maximum range: kVp=150, mA=600). The imaging was done in a single breath-holding period in craniocaudal direction.

The images transferred to computer media for interpretation. The criterion used to diagnose PE was as follows: luminal-filling defect in pulmonary arteries on at least two consecutive axial images, with a crescent or ring of contrast enhancement around partial filling defects.[11] Confounding artifacts like respiratory or cardiogenic motion artifact, overlying un-opacified pulmonary veins, bronchial wall thickening and peri bronchial lymph nodes, were removed by carefully analyzing regional anatomy and lung fields on lung and soft tissue windows.[12]

The Statistical Package for the Social Sciences (SPSS) version 23 was used for data analysis. Descriptive statistics were analyzed as mean ± standard deviation or median values for continuous variables and frequency percentages for nominal variables. Student t-test was used to test the significance of variation of mean and Pearson's chi-squared test was used for the assessment of nominal variables. ROC analyses were used to analyze area under the curve (AUC) and 95% CI to differentiate between groups with and without thromboembolism. Sensitivity, specificity, positive and negative prediction values as well as diagnostic accuracy rates were computed to assess whether D-dimer levels were helpful to distinguish between patients with and without thromboembolism based on the CTPA results. The *p*-value ≤0.05 was taken as statistically significant. The degree of association between d-dimer values and thromboembolism was estimated by Spearman's rank correlation analysis.

RESULTS

In total, 59 cases, which included 36 (61%) males and 23 (39%) females with mean age of 48.03 ± 18.06 years (range 23-85 years), underwent 128 slice spiral computed tomography pulmonary angiography

(CTPA) at AFIRI with a tentative diagnosis of pulmonary thromboembolism on the basis of clinical suspicion at the emergency reception. There were no significant differences in the age and gender distribution between groups with and without pulmonary embolism (p=0.187 and p=0.225, respectively). Frequency of consolidation, pulmonary vessel enlargement and pleural effusion in lung parenchyma was statistically higher in the group having thromboembolism as compared to group without thromboembolism (p=0.001, p-less than 0.001 and p=0.062, respectively) (Table-I). Frequency of raised D-dimer levels was not significantly different between the groups with and without pulmonary embolism diagnosed at CTPA (p:0.359) shown in Table-II.

Table-I: Demographics and clinical findings in cases with positive and negative pulmonary thromboembolism diagnosed on computed tomography pulmonary angiography.

Variables	Thrombo-embolism Not Seen (n=29)	Thrombo-embolism Present (n=30)	*p*-value
Age	44.86 ± 18.8	51.1 ± 17.07	0.187
Gender			
Male	20 (69%)	16 (53.3%)	0.225
Female	9 (31%)	14 (46.7%)	
Collapse/ consolidation	4 (13.8%)	24 (80%)	<0.001
Pleural effusion	5 (17.2%)	17 (56.7%)	0.001
Pulmonary vessel enlargement	3 (10.3%)	9 (30%)	0.062

Table-II: Comparison of D-dimer levels in groups with and without pulmonary thromboembolism diagnosed on CT pulmonary angiography.

Variables	Thrombo-embolism not Seen (n=29)	Thrombo-embolism Present (n=30)	*p*-value
D Dimer Level			
Normal (<250ng/ml)	20 (68.9%)	11 (36.6%)	0.359
Raised (>250ng/ml)	9 (31%)	19 (63.3%)	

ROC analysis showed D-Dimer levels to be not statistically significantly different in distinguishing groups with and without thromboembolism (AUC: 0.664, 95% CI: 0.500-0.788, p=0.57) (Figure).

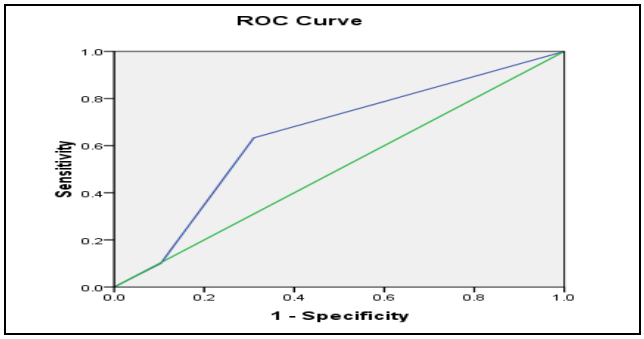

Figure: ROC Curve analysis for area under the curve (AUC) for D-dimer levels.

No significant correlation between D-dimer levels and CTPA findings was revealed by correlation test (r=0.279, p=0.128). The sensitivity, specificity, positive predictive value, negative predictive value as well as diagnostic accuracy for D-dimer levels in anticipating presence of thromboembolism were found to be 63.3%, 68.9%, 67.8%, 64.5% and 66.1%, respectively (Table-III).

Table-III: Diagnostic parameters of D-dimer levels in distinguishing groups with and without pulmonary thromboembolism diagnosed on computed tomography pulmonary angiography.

Parameters	Formulae	D-dimers
Number of Cases	n	59
Sensitivity	TP/(TP+FN)	19/30 (63.3%)
Specificity	TN/(TN+FP)	20/29 (68.9%)
Positive Predictive Value	TP/(TP+FP)	19/28 (67.8%)
Negative Predictive Value	TN/(FN+TN)	20/31 (64.5%)
Accuracy	(TP+TN)/(N)	39/59 (66.1%)

DISCUSSION

This was the first study of its kind in the clinical setup of Pakistan correlating the significance of plasma D dimer levels and CTPA in diagnosis of PE in cases reporting at the emergency reception. Acute pulmonary embolism is the most serious clinical presentation of venous thromboembolism.[13] The condition warrants an early diagnosis because it is common in clinical setting and easily treatable. Yet mortality rate remains towards the higher side because it is often missed.[4]

In a patient with suspicion of pulmonary embolism, the ideal diagnostic plan is to merge clinical evaluation, plasma D-dimer assessment and CTPA.[14] Low clinical probability and D-dimer values below the cut off level may exclude the possibility of PE, obviating the need for further tests. Nevertheless, in patients with intermediate or strong clinical suspicion of pulmonary embolism, no agreement is reached to exclude the diagnosis of PE even if D-dimer levels are within normal range.[4] In our study, we utilized the LATEX agglutination semi quantitative method for analysis of D dimer levels, due to its rapidity and easy availability in our setup. However, study by Crawford *et al*,[10] implies that it cannot be applied to make a definitive diagnosis of PE because of its low specificity with small sample sizes. This was also highlighted by low specificity in our study (68.9%). Low sensitivity, specificity and negative predictive value of D-dimer levels was also seen in patients at higher risk of PE in a study by Gupta *et al*.[15]

Study conducted by Nagel *et al*,[16] has shown that D-dimer measurement and clinical scores perform best in patients <50 years. Therefore, significant differences

in value thresholds are observed in patients >50 years of age. The quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays have a sensitivity of 95% or more. So they can be used with greater confidence instead of LATEX agglutination semi quantitative method to rule out PE in patients with a low or moderate pre-test probability. A negative ELISA D-dimer test along with clinical probability, can rule out PE without further investigation in approximately 30% of cases.[17] In the emergency set up the negative predictive value of D-dimers assay plays an important role in its utility for evaluation of PE. While D-dimer levels can correlate with the extent of PE on imaging, the use of these levels alone for diagnosing PE is still controversial as described by Gao *et al*.[1] Our study also provides similar interpretation with 36% of patients with normal D-dimer levels showing evidence of pulmonary embolism on CTPA.

CTPA is now deemed the imaging modality of choice in diagnosis of acute PE and remains superior to conventional pulmonary angiography and nuclear ventilation-perfusion (V/Q) study since it is fast, non invasive and now widely available. It is capable of directly visualizing emboli and may even provide an alternate diagnosis.[18] There are concerns over increased availability of CTPA leading to its overuse in diagnostic workup of patients having cardio-respiratory symptoms.[19] However, in case of positive D-dimers and high or a "likely" clinical probability, CT pulmonary angiography is now the recommended imaging technique.[20] The ability of CTPA to determine embolus burden, location (central or peripheral) and degree of obstruction also plays an important role in predicting short-term mortality of the disease,[21] hence highlighting its significance in the emergency setup.

The frequency of associated lung findings (pleural effusion, collapse/consolidation and pulmonary vessel enlargement) was in contrast to a similar study conducted by Gülşen *et al*,[4] hence highlighting variations in associated lung finding patterns of PE on CTPA in our setup. However, mean age of positive cases remained statistically higher as compared to negative cases similar to the study by Gülşen.

A retrospective design can be used to determine the optimal range of a laboratory parameter. Therefore, further research is required to assess the optimal cut-off range & reliability of LATEX agglutination semi quantitative method of D-dimers in diagnosis of PE in our population. Initiation of age adjusted D dimer levels in our setup as validated by various international studies is also a factor that needs consideration to improve patients' diagnostic outcome.

CTPA due to its high diagnostic accuracy remains the gold standard for detection and definitive diagnosis of PE. With relative limitations of plasma D dimer levels, CTPA represents the modality of choice in emergency to evaluate clinically suspicious patients of PE for early diagnosis and management of positive cases.

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LIMITATIONS OF STUDY

There were various limitations linked to our study. The sample size was relatively small. The study was retrospective in design, so it can be considered having selection and information bias. Information bias was likely minimal because D-dimer levels and reports with images of CTPA were reliably taken from patient's medical records.

CONCLUSION

When a patient comes to emergency reception with chest pain and dyspnea, performing D-Dimer levels only will not precisely rule out PE without CTPA evaluation, thus making CTPA a mandatory investigation for definite diagnosis. However, we suggest that further research may be carried out on the utility of plasma D dimer levels in our setup.

Conflict of Interest: None.

Authors' Contribution

UN & HN: Conception and design of study, article writing, data collection, and interpretation, AURS: Peer review and interpretation of data, RH: Data collectrin and interpretation, DHK: Statistical analysis.

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